THE INFLUENCE OF OBESITY ON OUTCOMES FOLLOWING TOTAL KNEE ARTHROPLASTY

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ABSTRACT

With the rising obesity and the increasing age of the population, a large proportion of patients who undergo Total Knee Arthroplasty (TKA) are obese. Knowing the health risks associated with obesity, it is important to determine if the outcomes of a TKA is compromised in obese patients.

Significant discrepancies in the findings of previous studies assessing the effect of body mass index (BMI) on TKA outcomes were observed in a literature review, thus making it difficult to confirm an effect of obesity measured as BMI on the outcomes after TKA. This thesis comprises two studies which further explored the effects of BMI and other body composition measures on the outcome of TKA.

1. The aim of a retrospective epidemiological study was to assess the effect of BMI on patient reported outcomes after TKA.

2. The aim of the prospective cohort study was to assess the effect of body composition, measured by waist circumference (WC), waist to hip ratio (WHR), bioelectrical impedance analysis (BIA), ultrasonography (US) and BMI, on patient reported outcomes after TKA.

It was concluded from these two studies that group division of obesity based on the classification of BMI greater or less than 30 kg/m^2 could not identify an effect of obesity on outcomes. However, on using BMI as a continuous variable, an adverse effect of BMI on knee function and overall physical health was evident for higher BMI ranges. Body composition measures of BIA and US did not detect an effect of obesity for any outcomes. Effect of obesity detected by BMI and WC was similar.

The negative association of BMI and outcomes observed was very weak across BMI ranges of 25-30 $kg/m^2$and a significant association was achieved due to poorer patient reported physical function (indicated by Short Form 12 and Oxford Knee Score questionnaires) in some cases with very high BMI values ($\geq$ 40 kg/m^2). In addition to this finding, the lack of group difference when outcomes were evaluated across a BMI of 30 kg/m^2in the two studies and the disparity between studies in the results when using a BMI classification of 30 kg/m^2 supported the conclusion that a BMI classification across a cut-off value of 30 kg/m^2 does not predict a poor result in obese after TKA.

However, because of the limited number of highly obese ($\geq$ 35kg/m^2) participants in both studies of the thesis and often in previous studies, no definite conclusions regarding the effect of higher obesity levels on the outcome of TKR can be drawn from the studies in this thesis. Adequately powered future studies with more morbidly obese participants could give more definitive answers to the effect of BMI and other measures of body composition on outcomes following TKA.

LIST OF KEYWORDS: Obesity, Total Knee Arthroplasty, Outcomes, Body Mass Index, Body composition.

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LIST OF ABBREVIATIONS

- AF: Atrial Fibrillation
- BF%: Body Fat %
- BIA: Bioelectrical Impedance Analysis
- BMI: Body Mass Index
- CAD: Coronary Artery Disease
- CI: Confidence Interval
- CT: Computerised Tomography
- DVT: Deep Vein Thrombosis
- DXA: Dual X-ray Absorptiometry
- ECW: Extra Cellular Water
- EULAR: European League of Associations for Rheumatology
- FFM: Fat Free Mass
- HRQoL: Health Related Quality of Life
- HSS: Hospital for Special Surgery Score
- HW: Hydrostatic Weighing
- ICW: Intra Cellular Water
- Kg: Kilogram
- KHz: Kilo Hertz
- KSS: Knee Society Score
- LVF: Left Ventricular Failure
- m: Metre
- mA: Milli Ampere
- mm: Millimetre
- MI: Myocardial Infarction
- MRI: Magnetic Resonance Imaging
- NCC-CC: National Collaborating Centre for Chronic Conditions
- NSAID: Non Steriodal Anti – Inflammatory Drugs
- NHP: Nottingham Health Profile questionniare
- OA: Osteoarthritis
- OKS: Oxford Knee Score
- ORSI: Osteoarthritis Research Society International
- RCT: Randomised Controlled Trials
- SF12: Short Form 12 Health Survey
- SF36: Short Form 36 Health Survey
- TBW: Total Body Water
- THR: Total Hip Replacement/Arthroplasty
- TIA: Transient Ischemic Attack
- TKA: Total Knee Arthroplasty
- UK: United Kingdom
- US: Ultrasound
- WC: Waist Circumference
- WHO: World Health Organization
- WHR: Waist to Hip Ratio
- WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

INTRODUCTION TO THESIS

The prevalence of obesity and overweight in the general population is rising worldwide and one of the common and disabling problems secondary to obesity is the development and progression of osteoarthritis. Large scale studies such as the Farmingham study (Felson et al. 1988), studies by Lohmander et al. (2009) and Wang et al. (2009) among others have found evidence of a strong positive association of obesity with the risk of knee osteoarthritis and the progression of the disease to a stage where a total knee arthroplasty is required.

Not surprisingly, with the increased prevalence of obesity and the increasing age of the population, impact of obesity on the progression of osteoarthritis is such that the proportion of obese patients undergoing TKA is high and is increasing over the years. Total knee arthroplasty is one of the most widely performed surgical operations and has a high success rate in improving the function and quality of life in patients with knee osteoarthritis. With the known risk of obesity with surgical complications, operative difficulties, whether or not the success in improving joint function and patient's quality of life by TKA is affected by obesity such that obese patients are predisposed to adverse outcomes, has been a topic of much debate. There have been doubts regarding the safety, prudence and cost effectiveness of total knee arthroplasty in obese patients. Moreover, it has been reported that obese patients present for total knee arthroplasty at a younger age (Namba et al. 2005;Kulkarni et al. 2011). Obesity at a younger age combined with the increasing life span of the population would imply that obese patients would have a greater chance in the longer term of having a revision surgery which are technically and economically more demanding procedures.

Considering these perceived risks and cost implications, obese patients are specifically advised and informed of the possibility of an increased risk of complications and possible poor outcomes. In some health care trusts, patients are encouraged to lose weight prior to

surgery, for example, in the Oxfordshire NHS trust, patients with BMI 35-40 kg/m^2 are advised to join a weight loss programme and for patients with BMI $\geq$40kg/m^2, it is mandatory to undergo a weight loss programme.

Obesity in the U.K. has been found to be more prevalent in the lower socio-economic groups (National Obesity Observatory 2010) and for these patients' weight loss and access to a weight loss programmes are more challenging. If patients are advised to join a weight loss programme prior to surgery, waiting time before surgery would increase during which their osteoarthritic disability is likely to further increase. With increasing financial pressures, some primary care trusts have proposed barring of total knee arthroplasty procedures in obese with BMI $\geq$30 kg/m^2 (Davis and Porteous 2007).

Previous research on the effect of obesity on success or results of total knee arthroplasty has been inconclusive due to considerable differences between the findings of the studies. Some studies have found comparable results of the surgery between obese and non-obese (Stickles et al. 2001; Amin et al. 2006, Nunez et al. 2010), while others have shown evidence for compromised results of the surgery in obese (Foran et al. 2004a; Foran et al.; 2004b; Jackson et al. 2009; Dowsey et al. 2010). The two main aspects in a research evaluating the effects of obesity on TKA outcomes are; how obesity is defined and how outcomes are measured. A range of outcomes that are both assessed by the investigator and reported by patients have been employed to define outcomes in studies. In the early studies in this area, outcomes have been primarily measured by the investigator. The recognition of the importance of patient perceived outcomes in providing a complete picture of the results has led to the assessment of obese and non-obese patients' perception of the outcomes of their total knee arthroplasty.

Definition of obesity in the literature assessing TKA outcomes in obese patients so far has been based on body weight and body mass index (BMI). However, the association between obesity and a joint with osteoarthritis has been shown to be more complex than just as function of body weight and body mass. Since measures of body weight and BMI are limited in their assessment of true obesity or adiposity, it still remains to be explored if other aspects of body composition show any effect on TKA outcomes.

Therefore, the current thesis addresses the following two main research questions:

1. Does obesity as estimated by body mass index affect total knee arthroplasty outcomes?
2. Does obesity measured by a range of body composition measurement methods in addition to body mass index affect total knee arthroplasty outcomes?

These research questions have been approached in this thesis in the following three parts:

1. Literature review, with the aim: to critically evaluate previous research studies assessing the effect of obesity on total knee arthroplasty outcomes and derive conclusion from the evidence regarding the effect of BMI on post-operative complications, joint function, overall physical function and prosthetic longevity after total knee arthroplasty.
2. Retrospective epidemiological study, with the aim: to evaluate the effect of BMI on the clinical and patient perceived outcomes for up to one year following a total knee arthroplasty.
3. Prospective cohort study, with the aim: to evaluate the effect of obesity as measured by five body composition measurement methods on the clinical and patient perceived outcomes for up to one year following a total knee arthroplasty.

OVERVIEW OF THE CHAPTERS

Chapter one provides a summary of the background literature on osteoarthritis and weight loss as an intervention for the treatment of osteoarthritis. The majority of people undergoing TKA have an underlying diagnosis of osteoarthritis and only small percentages in both studies were diagnosed with rheumatoid arthritis.

Chapter two provides a summary of the background literature on total knee arthroplasty as an intervention for treating end stage knee disease and its prevalence. The chapter discusses the outcomes after surgery and the instruments used to measure these outcomes.

Chapter three discusses the literature assessing the association of obesity with knee osteoarthritis and provides a brief overview of the prevalence of obesity in the general population and among total knee arthroplasty patients and methods of measurement of body composition.

Chapter four presents the literature review of the effect of obesity on total knee arthroplasty outcomes. This includes the background to the literature review, evaluation of previous studies to assess the effect of body mass index on post-operative complications, functional outcomes and prosthetic longevity and finally, conclusions of the literature review. Discussions of other factors which may be associated with obesity and may have an effect on outcomes are also given in this chapter.

Chapter five presents the retrospective epidemiological evaluation of the effect of body mass index on clinical outcomes (post-operative complications); patient perceived knee function (measured by oxford knee score questionnaire) and patient perceived quality of life (measured by Short Form 12 health survey) at six months and one year after total knee arthroplasty. The chapter includes a background and aim of the study, methods followed to acquire data, analysis and reporting of the results and a discussion of the findings.

Chapter six (methods) seven (inter and intra-rater reliability of the measurement of fat thickness and intra-rater reliability of the measurement of body fat percentage) and eight (results and discussion) present the prospective cohort study assessing the effect of various measures of body composition on the clinical and functional outcomes after TKA. The body composition measures are body mass index, waist circumference, waist to hip ratio, fat percentage as measured by bioelectrical impedance analysis, and fat thickness as measured by ultrasonography.). Clinical and functional outcomes, post-operative complications; patient perceived knee function (measured by oxford knee score questionnaire), patient perceived quality of life (measured by Short Form 12 health survey), pain perception (measured by visual analogue pain scale) were assessed at six weeks, six months and one year after total knee arthroplasty.

Chapter nine integrates and summarizes the main findings of the thesis, implications of the findings, future research suggestions and the conclusion of the thesis.

CHAPTER 1: OSTEOARTHRITIS

1.1. Chapter Overview

This chapter begins with the definitions of osteoarthritis followed by the current prevalence of knee osteoarthritis, its clinical features and impairment of function caused by osteoarthritis. Etiology of osteoarthritis is then discussed followed by current opinions with regard to the treatment of osteoarthritis. Finally, a section on weight loss as an intervention for knee osteoarthritis is presented.

1.2. Defining Osteoarthritis

Early definitions of osteoarthritis (OA) in 1904 by Goldthwaite describe it as bone hypertrophy with focal cartilage damage to allow differentiation of osteoarthritis from other forms of arthritis (McAlindon and Dieppe 1989). Since then, there have been multiple definitions of osteoarthritis, and these definitions can be based around clinical features, pathological findings or radiographic features (Spector et al. 1993). While clinically it may be known what constitutes osteoarthritis, there is a lack of general consensus on a precise definition of osteoarthritis for epidemiologic and outcomes studies (Spector et al. 1993; Lanyon et al. 1998). A definition of osteoarthritis encompassing all of its three main domains of pain, disability and structural changes is difficult because of the lack of agreement between these domains (Lanyon et al. 1998). This lack of association seen between the structural changes (as assessed by radiography) and symptoms experienced by the patient is striking. For example, a recent systematic review of the discordance between clinical (symptomatic) and radiographic knee osteoarthritis

found that, in those with radiographic changes of osteoarthritis, the proportion of patients experiencing pain ranged from 15% - 81%, while, 15% - 76% of those with knee pain were found to have radiographic changes of osteoarthritis (Bedson and Croft 2008).

Thus, osteoarthritis can be asymptomatic and the association between the joint anatomical changes and the symptoms is weak. Furthermore, the association between the progression of structural changes and the changes in symptom is also weak (Brandt 2009).

A more inclusive definition developed recently by a panel of experts is as follows:

> 'OA diseases are a result of both mechanical and biological events that destabilise the normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix and subchondral bone. Although they may be initiated by multiple factors, including genetic, developmental, metabolic and traumatic, OA diseases involve all the tissues of the diarthrodial joint. Ultimately OA diseases are manifested by morphologic, biochemical, molecular and biomechanical changes of both cell and matrix which lead to softening, fibrillation, ulceration, loss of articular cartilage, sclerosis, eburnation of subchondral bone, osteophytes and subchondral cysts. When clinically evident, OA diseases are characterised by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable degrees of inflammation without systemic effects.'
>
> (Kuettner and Goldberg 1995, cited in Sharma and Kapoor 2007, pp. 3)

Brandt (2009) however argues that the above definition gives a general emphasis on joint damage and particular indication to articular cartilage loss but fails to recognize that osteoarthritis represents the joints attempt to repair the damage cause by local biomechanical problems. Brandt (2009) defines osteoarthritis as the failure of the joint caused due to mechanical stress on the joint tissues. Due to this mechanical abnormality, the body's innate mechanism to repair the damaged tissue is ineffective.

Based on evidence to date, the latest consensus on defining osteoarthritis has further evolved to:

> 'OA is usually a progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial tissues, including articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves or

synovium. This ultimately results in breakdown of cartilage and bone, leading to symptoms of pain stiffness and functional disability. Abnormal intra-articular stress and failure of repair may arise as results of biomechanical, biochemical and/or genetic factors.'

(Lane et al. 2011).

1.3. Osteoarthritis signs and symptoms

1.3.1 Prevalence

Osteoarthritis is one of the leading causes of disability especially in the elderly (Peat et al. 2001). The above discussed discordance between symptoms and structural changes of osteoarthritis also affect the estimation of prevalence of osteoarthritis. Peat et al. (2001) in their review of the community burden of knee osteoarthritis point out that this need for distinction between radiographic changes and symptoms is evident from the results of population surveys such that 50% of the individuals with knee osteoarthritis shown by radiographic evidence had no knee pain. Moreover, in 50% of those who complained of knee pain, no definite radiographic evidence of OA was seen. Thus, prevalence of osteoarthritis would depend much on how osteoarthritis is defined i.e., if the population prevalence estimates are based on pain, disability and/or radiographic changes.

The prevalence of osteoarthritis does have a striking correlation with age such that regardless of the definition of osteoarthritis it is highly uncommon under the age of 40 years and highly prevalent after 60 years of age (Felson 2003). Current data on knee osteoarthritis in the United Kingdom show that one in every five persons between the ages of 50-59 years has painful knee osteoarthritis and this increases to one in every two persons with painful knee osteoarthritis in persons above the age of 80 years, thus clearly showing an increasing prevalence with age (Arthritis Research U.K. 2008).

A higher prevalence of knee osteoarthritis has been seen in women and the gender disparity rises with increasing age and is suggested to be consistent with the role of post-menopausal hormone deficiency (Felson 2003)

1.3.2 Clinical features

Plain radiography is considered the gold standard in imaging for osteoarthritis. Radiography has the advantage that high resolution images in weight bearing position can be easily obtained (Bijlsma et al. 2011).

The radiographic criteria for OA proposed by Kellgren and Lawrence (1957) were accepted by the World Health Organization (WHO) in 1961 as the standard for radiographic grading of osteoarthritis and have since been used widely for epidemiological studies (Altman et al. 1986; Bijlsma et al. 2011). The Kellgren and Lawrence scale focuses on the following radiographic features of osteoarthritis: osteophyte formation, joint space narrowing, and bone sclerosis. Combinations of these changes were considered to develop an ordinal scale to grade the severity of osteoarthritis (Bijlsma et al. 2011). Limitations of this grading have been noted since, the primary being that no weight bearing positions were used for knee radiographs thus limiting the accurate assessment of the degree of joint space narrowing. Several groups since have developed reliable grading schema for the knee, in an attempt to overcome these limitations of a global grading scale (Flores and Hochberg 2003).

According to the recommendations of clinical diagnosis developed by European League of Associations for Rheumatology (EULAR, Zhang et al. 2010), diagnosis of knee OA can be made on the basis of:

a. background risk (population prevalence of knee OA)
b. patients risk factors (e.g., age, gender, BMI, occupation)
c. symptoms (persistent knee pain, stiffness of the joint, functional limitation)
d. physical examination (crepitus, restricted movement, bony enlargement)
e. plain radiographs, to be used as an adjunct for the purpose of diagnosis.

These recommendations were made on the basis of expert opinion and systematic review. While there is no universally applicable reference standard for knee osteoarthritis diagnosis, these recommendations were made on a combination of radiographic evidence and clinical features. However, if above diagnosis differ in atypical patients younger than 40 years of age was not examined by the panel.

The first point of contact of an osteoarthritis patient with the doctors is usually due to pain which is the first and the predominant symptom (Bijlsma et al. 2011). The nature of pain is intermittent and aggravates on weight bearing (Bijlsma et al. 2011) and stiffness in the joints is experienced either in the morning after a period of inactivity or in the evening. O'Reily and Doherty (2003) also list tenderness, joint deformity and instability as possible symptoms.

The impact of osteoarthritis on specific functions is specific to the joint involved. The most common limitation caused by knee osteoarthritis is on mobility. In fact, the difficulty in walking and stair climbing due to osteoarthritis of the knee is as great as that attributable to cardio vascular disease and greater than any other condition in an elderly person (Felson 2000), clearly a substantial impact on function. Creamer et al. (2003) developed a model to assess the determinants of functional impairment in knee osteoarthritis patients using self-report pain and function measure and found that pain severity, obesity and helplessness accounted for 59.5% variance in the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC).

Additionally, anxiety, depression and inability to sleep associated with the symptoms may contribute to disability and diminish the quality of life of the patient (Bijlsma et al. 2011).Factors linked to the risk of physical disability in osteoarthritis are pain (McAlindon and Dieppe 1989; Creamer et al. 2000), psychosocial factors (O'Reilly and Doherty 2003), muscle weakness, poor aerobic capacity (Sharma et al. 2003), radiographic disease severity (Guccione et al. 1990).

The impact of osteoarthritis is not just limited to the physical performance of the individual. Disability is defined as 'the impairment performance of socially defined life tasks in a typical socio cultural and physical environment.'(Jette et al. 2002 cited in

Sharma et al. 2003). While arthritis primarily limits the physical functioning of the individual, the concept of function also includes psychological and social functioning. Although these are distinct dimensions, they influence each other in that the physical function may influence the psychological and social functions and physical function may in turn be influenced by psychological and social function (Guccione1997).

While the role of osteoarthritis in consequent disability of a person seems obvious enough, Guccione (1997) points to factors which complicate the study of the link of osteoarthritis to disability. Firstly, radiographic evidence of OA does not necessarily mean it is symptomatic; therefore, it is important to consider whether the presence of arthritis is regarded as problematic by the patient or the clinician. Secondly, the prevalence of the disease may have led to it being too common and not as serious as other ailments of the geriatric population. And finally, measurement of disability due to osteoarthritis is also affected by other comorbidity present in the patient.

1.4. Etiology of osteoarthritis

Susceptibility to osteoarthritis is due to interplay of local and systemic factors (Jordan et al. 2000). Felson (2003) suggests that the most common local factor leading to osteoarthritis is a previous injury to the joint such that a major injury to the joint can damage a number of structures within it, altering its biomechanics and the stresses placed across the joint and thus making it vulnerable. The Framingham study (Felson et al. 1988), found a statistically significant relative risk of the later development of osteoarthritis in males and females with a history of major injury to the knee (relative risk of 3.5 and 2.2 respectively). Another study by Roos et al. (1995), which assessed the influence of time and age on the development of osteoarthritis after knee injury, concludes that development of osteoarthritis after injury is faster in older patients than in younger ones. Therefore, it is suggested that a major injury to the joint in itself can lead

to osteoarthritis of the joint; however, more commonly it is the effect of an injury on the joint in a person with a systemic vulnerability depending on their age and other factors which causes OA. Thus, indicating a local and systemic interplay leading to osteoarthritis in an individual (Felson et al. 2003).

Other factors affecting the joint include quadriceps muscle weakness, obesity, and repeated use/strain of the joint due to occupational, athletic activities. Earlier for certain factors like obesity it was not clear if obesity preceded OA or was a consequence of the disability and immobility caused by OA. It is now known that being overweight precedes the development of OA and also increases the likelihood of the disease progression (Felson et al. 1988). The effect of obesity on OA has been further discussed in Chapter 3.

Felson et al. (2000) in an evidence update review listed other local vulnerabilities which include:

a. Knee laxity: Greater varus-valgus laxity of the knee was seen in those with osteoarthritis than older control knees without arthritis. Moreover, varus-valgus laxity increases with age suggests the possibility that a proportion of the laxity preceded the disease and could have predisposed to the disease (Sharma et al.1999).
b. Mal-alignment: There is paucity of evidence regarding whether mal-alignment of the joint is an independent risk factor for the development of osteoarthritis. However, it has been shown that a varus alignment in primary osteoarthritis can increase the risk of a medial progression and a valgus alignment can increase the risk of lateral progression (adjusted odd ratio of 4.09 and 4.89 respectively) (Sharma et al. 2001)
c. Proprioception: Proprioceptive accuracy at the knee declined with age and was worse in osteoarthritis patients when compared to age matched controls in a study by Sharma et al. (1997). The decline in proprioception reduces the ability to maintain joint stability in dynamic conditions.

While these above factors are essentially alterations of the mechanical environment of the joint which adversely affects the load distribution across the joint, systemic factors which increase the risk of osteoarthritis include age, gender, hormonal status, bone density, probable nutritional deficiencies and genetic influences (Felson et al. 2000).

1.5. Osteoarthritis treatment concepts

The recognition of osteoarthritis as a complex disease and the fact that there is a great degree of variation in the clinical and structural characteristics of osteoarthritis in different individuals has restricted the development of a generic plan for the management of osteoarthritis (Bjilsma et al. 2011). However, there is some consensus on the central objectives of the management of osteoarthritis in the recommendations made by expert panels such as EULAR; Osteoarthritis Research Society International (ORSI) and National Collaborating Centre for Chronic Conditions (NCC-CC). The three main treatment modalities recommended by NCC-CC (2008) are:

a. Non pharmacologic management including patient education and recommendations for lifestyle change, exercise, weight reduction, joint protection measures such as insoles, braces, activity pacing and treatment modalities such as transcutaneous electrical nerve stimulation, ultrasound, heat and ice.
b. Pharmacological management includes paracetamol, topical Non-Steroidal Anti Inflammatory Drugs (NSAID), oral NSAID, opioid analgesic. Intra-articular corticosteroids are recommended as an adjunct for pain relief and can be effective during periods of inflammatory flares.
c. Surgical options include total knee arthroplasty when the above non-surgical management has failed to reduce symptoms which have made a substantial impact on the patient's quality of life. Surgical lavage and debridement have not been generally advised as a part of osteoarthritic management.

Pain and functional limitations are the main problems affecting an OA patient for which they seek treatment. However, the disparity between pain, disability and radiographic changes of OA lead to a considerable variation in pain and disability between individuals and this is compounded by factors such as age, comorbidity, personality and expectations of health care delivery (Brandt et al. 2003). This has led to a shift to a holistic approach to the management of osteoarthritis tailored to individual needs of the patients (NCC-CC 2008).

1.6. Weight loss as an intervention for knee osteoarthritis

Significant association of body mass/body weight with the risk and the progression of osteoarthritis have been found in several studies (Hartz et al. 1986;Felson et al. 1988; Sturmer et al. 2000). This will be discussed in further detail in Chapter 3. Two high quality randomized controlled trials (RCT) undertaken to assess the effects of weight loss programmes on the symptoms of OA conclude that weight loss does results in improvement in pain and function in knee osteoarthritis patients (Messier et al. 2004;Christensenet al. 2005). Short term weight loss was assessed by Christensen et al. (2005) over a period of eight weeks evaluating a low energy diet group versus a control diet group. The study saw significant improvement in symptoms (measured by WOMAC scores) in the low energy diet group and found that a 10% reduction in weight lead to a 28% improvement in function. Messier et al. (2004) conducted a four arm RCT comparing control, diet only, exercise only, diet plus exercise groups over 18 months and found that the combination of diet plus exercise had the most beneficial effect on function and pain. The recommendation of weight loss as a therapeutic intervention for knee osteoarthritis patients is further supported by meta-analysis of four RCTs conducted by Christensen et al. (2007) (including the above mentioned two RCTs) They noted that for an average reduction of 6.1 kg, the pooled effect size (ES) for improvement in pain and disability was 0.20 (95% CI 0 to 0.39; p=0.05) and 0.23 (95% CI 0.04 to 0.42; p=0.02) respectively. The diversity across the studies was substantial especially considering the different approaches used for weight loss and the duration of the study. Meta regression models used in the analysis to understand the dose response effect for clinical practice found that the prediction of reduction in pain resulting from weight loss was inconsistent but weight loss greater than 5.1% at the rate of 0.24% per week would result in a significant reduction in disability. Supported by this evidence and expert clinical opinion, weight loss for overweight knee osteoarthritis patients was recommended as a treatment modality for reducing symptoms of knee osteoarthritis (Jordan et al. 2003; Zhang et al. 2010).

1.7. Chapter summary

To summarize, over the last decade, the definition of osteoarthritis has evolved from ‘hypertrophic arthritis’ to the recognition of osteoarthritis as a complex disease with no common pathological pathway. Osteoarthritis is now generally recognized as a progressive disease manifested in the structural changes in the joint and an illness reflected in pain, functional limitation and deteriorating quality of life in the patient’s experience of living with osteoarthritis. One of the leading causes of disability, osteoarthritis is highly prevalent after the age of 60 years. Significant association of knee osteoarthritis with body weight and evidence of reduction in symptoms with weight loss has led to weight loss being is one of the treatment modalities recommended for reducing symptoms of knee osteoarthritis. On failure of pharmacological and non-pharmacological management of symptoms, a total knee arthroplasty is the recommended line of treatment.

CHAPTER 2: TOTAL KNEE ARTHROPLASTY

2.1.Chapter overview

This chapter presents an overview of total knee arthroplasty (TKA) as an intervention for end stage osteoarthritis and its prevalence. Outcomes after TKA are presented followed by a discussion of the measurement of outcomes after TKA.

2.2. Introduction

Total Knee Arthroplasty has become a highly successful orthopedic procedure for joint reconstruction affording pain relief, mobility and functional improvement in patients where other non-surgical interventions for the management of arthritis have failed (Harwin2002).

Attempts at treating diseased joints with prosthetic replacements which started over a century ago were initially met with failure; primarily due to unsuitable implant material, surgical techniques, sepsis and lack of proper indications (Knutson 2003). The evolution of TKA especially benefited from advances in the prevention of infection; implant material, prosthetic fixation to the bone, surgical instrumentation and knowledge of biomechanics of the knee (Deroche 2008). The modern tricompartmental (total) knee prosthesis was essentially metal implants including an anatomic shaped femoral component, the tibial component as a cemented metal tray on which sits a High Density Polyethylene (HDPE) component and a patellar articulation (Knutson 2003).

Joint arthroplasty is an intervention for patients with radiographical changes in the knee suffering from severe joint pain and disability that has had a substantial effect on their quality of life and is refractory to non-surgical management (British Orthopedic Association report 1999). Relative indications include progressive deformity and instability (British Orthopedic Association report 1999). Age and comorbidity are factors taken into consideration to assess risk versus benefits, which may rule out the surgery for particular patients (British Orthopedic Association report 1999).

Although, the operation was only offered to older patients with limited activity levels, it has now been shown to be also effective and durable for younger and more active patients (Harwin 2002). The surgery is considered ideally suitable for patients above the age of 60 years as the implant is more likely to last for the rest of the patient's life (Harwin 2002).Being an elective procedure, patients' motivation and their willingness or reluctance to undergo the surgery also influence whether or not patients undergo surgery.

2.3. Rate of TKA

Osteoarthritis is the most frequent cause of rheumatic complaints among all joint specific diseases (Brandt 2009). Recent estimates indicate that within the United Kingdom (U.K.), more than one million patients consult with their general practitioner each year for osteoarthritis (Arthritis research U.K., 2008). Over all, more than six million individuals have painful OA in one or both knees (Arthritis research U.K., 2008).

The increasing prevalance of OA and an increasing average age of the population may account for the consistently rising rate of TKA. In addition, changes in medical practice, improvement in technology, increasing availability,acceptance and satisfaction with the surgery may also account for some of this increase in the rate of TKA (Mehrotra et al. 2005). A survery of the primary TKA in the USA from 1990 to 2002, found tripling of the number of primary TKAover the 13 year period, an increase which was more

pronounced than that for primary total hip arthroplasty (Kurtz et al. 2005). Latest fugures for England and Wales reveal a total of 86,067 primary TKA in years 2010/11, a 10% increase from year 2009/10 (National Joint Registry for England and Wales 2011). For Scotland 6,884 primary knee replacements were performed in 2008/09, an increase from 6160 operations performed in 2007/08 (Scottish Arthroplasty Report 2010).

2.4. Outcomes after TKA

Total knee arthroplasty has been long reported to be an effective and safe intervention offering significant pain relief and improvement in function for patients with advanced arthritis (Callahan et al. 1994; Heck et al. 1998). Meta-analysis of 130 studies reporting patient outcomes on 154 cohorts by Callahan et al. (1994) reported that 52% to 100% of the patients had good to excellent outcomes (weighted mean of 89.3%) in terms of pain relief and mobility measured by the Global Rating Scale at a mean follow up of 4.1 years. TKA was shown to be an effective procedure with relatively low risk of serious complications and mortality in the majority of patients. Similarly, marked improvements in physical function scores using WOMAC and Short Form 36 Health Survey (SF-36) were reported in a community based study, showing that at two years, TKA was an effective procedure in a community setting (Heck et al. 1998).

Survivorship of the knee prosthesis in a large study of 11,606 primary TKA showed survivorship of 91% at ten years, 84% at 15 years, decreasing to 78% at 20 years (Rand et al. 2003). Revision rates reported from the most recent data analyzed from the joint registries of six countries and clinical studies were projected at 6% after five years and 12% after ten years (Labek et al. 2011). A U.K. based study analyzing 4606 TKA's, observed that greater than 90% of the prosthesis survived at 15 years follow up (Roberts et al. 2007). Females are reported to less likely undergo revision surgery while younger patients (aged less than 55 years) had a lower prosthetic survival rate of 87% at 15 years

(Roberts et al. 2007). They noted that failure observed due to aseptic loosening was seen to be constant over the 15 years follow up; failure due to infection was common within a year of the surgery, while, failure of the polyethylene was seen at approximately eight years post-operatively.

It has been recognized that patient expectations determine the success of an intervention and the patient's perception of the outcome of the surgery is considered essential in the evaluation of treatment (Weiss et al. 2002). Various questionnaires have been used in order to measure patient's perception of their function and pain after TKA, both specific to the knee joint such as WOMAC, Oxford Knee Score (OKS), and those measuring the overall health related quality of life such as the Short Form 36 Health Survey. Substantial improvements in the scores for physical health, such as those for pain and knee function have been reported by several studies (Xie et al. 2010;Ethgenet al. 2004; Nilsdotter et al. 2009). Nilsdotter et al. (2009) observed that while there was clinically significant improvement in 88% and 81% of patients respectively for pain and activities of daily living at five years postoperatively, the maximum improvement was seen at one year post-operatively indicating some decline in function from one to five years after TKA. The authors suggest the role of musculoskeletal and other comorbidity and irreversible damage of the disease (OA) in causing deterioration in function.

Total knee arthroplasty patients participate in a wide range of activities (Nilsdotter et al. 2009; Noble et al. 2005; Weiss et al. 2002). There is a high correlation between the importance of an activity and the frequency of participation indicating that knee replacement enables patients to perform activities they consider important or that patients perform these activities irrespective of the function achieved in their knee (Weiss et al. 2002). In their sample of 176 patients, Weiss et al. (2002) found stretching exercise (56%), kneeling (52%) and gardening (50%) were activities graded most important to patients in their assessment. However more than 75% of the patients who squatted and kneeled reported limitations. On comparing TKA patients with age matched controls with no previous knee disorders, Noble et al. (2005) observed that overall, 52% of the TKA patients reported some limitation in functional activity compared to 22% of subjects with no previous knee disorders and as the activities became more demanding, the gap

between the two groups widened. The activities in which the control group did better that the TKA patients included kneeling, squatting, stretching, gardening, tennis, dancing. Thus, although this procedure restores the patient's ability to do routine tasks, deficit still remain for functional tasks that are important to the patient especially those involving kneeling and squatting (Noble et al. 2005).

Total knee arthroplasty has considerably advanced in terms of surgical techniques, prosthetic fixation and a multitude of different prosthesis with varying degrees of tibio femoral conformity (Jordan et al. 2003). Despite these advancements in TKA as an intervention, knees that have undergone total knee replacement cannot replicate the functional status of a healthy, uninjured adult knee (Dye 2005). As seen by Noble et al. (2005), for biomechanically demanding activities such as kneeling, squatting, moving laterally, turning and cutting, carrying loads, TKA patients experience substantial functional impairment compared to the age and gender matched individuals suggesting further room for improvement in surgical technique and prosthetic design. In addition, these functional deficits will also exist because of the irreversible effects of the disease and factors predisposing some individuals to joint degeneration (Noble et al. 2005; Nilsdotter et al. 2009).

In a qualitative and systematic review of health related quality of life (HRQoL) in total hip and knee arthroplasty patients, the greatest improvement in HRQoL was seen in the first three to six months after surgery. Substantial improvements though noted for physical health scores, the improvement in social health and mental health was less obvious. It is argued that these dimensions are not related to knee surgery, and that surgery may relieve a specific complaint but it might not enhance the overall quality of life. On the other hand, it has been found that the pre-operative mental health was a significant factor affecting the post TKA function (Escobar et al. 2007, Ayers et al. 2005) Also, other factors such as comorbidity, use of medication, and social support are likely influence the success or failure of the operation in improving the HRQoL. An interview of ten TKA patients six months after their surgery, found that patients had a strong desire to report the outcomes in positive terms initially, despite some pain and disability remaining after the surgery (Woolhead et al. 2005). While pleased that an intervention

had been carried out to relieve pain and disability and that they were able to do more activities than before, patients try to rationalize and reason in an attempt to diminish the disappointment with the residual pain. The predominant rationalization was self-blame for the continued pain and immobility which the authors suggest may represent an attempt to take control over the outcomes. Thus while quantitative studies may report good or excellent outcomes after TKA in majority of the patients, it should be noted that there exists marked disparity between the patient's evaluations of the outcomes, qualitatively or through a self-report outcomes after TKA and that done by a clinician (Wylde et al. 2007).

The available literature suggests that overall; TKA is a valuable intervention in relieving pain and restoring function. However, the evidence of the effectiveness of TKA is based on observational study and not randomized controlled trials. Comparison of TKA with placebo or other treatment methods using a well-designed study is often impossible due to ethical considerations. Blinding of investigator is not feasible in a clinical setting. Furthermore, wide variation in the indications for TKA, types of prosthesis and variation in availability of TKA in different areas affect comparison of TKA outcomes from the literature.

2.5. Measure of the outcomes after total knee arthroplasty

There are many approaches to surgical outcome measurement by a diverse range of disciplines which may or may not be directly involved in patients' medical care Thus the term outcome of a surgical procedure, though in some cases may be synonymous with the result of a surgery, is a much more multifaceted and complex issue.. The assessment and documentation of the results of the surgery in terms of impressions of symptoms, functional status, physical examinations and laboratory or radiographic findings, the

relative importance of these assessments depends on who is performing the evaluation; the surgeon, the patients or the health service researchers (Johansen 2002)

2.5.1. Hospital for Special Surgery knee rating score (HSS) and American Knee Society's Clinical Rating System (KSS)

With the evolution of a multitude of prostheses, surgical approaches, a number of rating systems to evaluate knee function have been developed. A review of the rating systems identified 34 different rating systems in the orthopaedic literature between 1972 and 1992 (Drake et al. 1994). Of these the most widely used were Hospital for Special Surgery knee rating score (HSS) and American Knee Society's Clinical Rating System (KSS) (Drake et al. 1994). The HSS was developed in 1976 (Insall et al. 1976) and used widely for its ease of use; weighing primarily on pain, function and range of movement. Insall et al. (1989) later published the American Knee Society's Clinical Rating System (KSS) in an attempt correct the deficiencies of the HSS score. The KSS separated the knee function from overall patient function so as to enable knee function to not be subject to deterioration by comorbidity The KSS though not validated at the time of publication has been validated and tested for reliability and responsiveness to change against WOMAC and SF36 showing adequate construct validity but poor internal consistency (Lingard et al. 2001). Also, in terms of inter-observer reliability; Bach et al. (2002) found that the knee score had poor reproducibility. However, the KSS is now one of the most commonly used rating systems for the knee in the U.K. These scoring systems are easy to use and understandable to the clinician; however, they do not represent the full range of a patient's lifestyle. Both KSS and HSS are evaluations done by an observer using a combination of interview and physical examination.

Details of the psychometric properties of HSS and KSS are as shown in Table 1.

2.5.2. Patient perceived outcomes

Early literature measured the effectiveness of TKA primarily on the basis of its technical success in terms of prosthesis longevity, physician defined pain relief and function. It is recognized that there exists disparity between the physician's and patient's evaluation of the outcomes, especially when the patients were dissatisfied with the surgery (Wright et al. 1994). TKA is a procedure performed primarily with the aim to achieve pain relief and restore function and the goals of the patients will differ with respect to the post-operative function and activity. However, these patient goals and whether the patient thinks that he or she has significant residual disability determine the success of the surgery. Therefore patients' perspectives on the outcomes are considered an important component of evaluation.

Patient self-assessment techniques are generally simple and readily accepted by patients (Heike et al. 2003). The techniques mostly involve questionnaires which are self-administered by the patients or administered through an interviewer. A number of patient reported questionnaires have been developed in clinical research with excellent psychometric properties measuring knee specific function or generic health status. However, a problem with these techniques is that the perception of change derives its significance from the comparison between the starting or the pre-operative state and the post-operative state (Heike et al. 2003). Therefore for a persons with poor starting state, a relatively small change from pre-operative to post-operative status would be perceived as a clinically significant change while for those with a better pre-operative state, the same amount of change will not be considered by the patient as a significant change.

Various patient-reported instruments are available to assess TKA outcomes and are referred to as generic when developed for general population and joint specific when developed for a particular joint condition. Among the self-assessed knee scoring systems, the most widely used are the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and the Short Form 36 (SF36). While WOMAC was originally developed to assess the effectiveness of NSAIDs as treatment for osteoarthritis (Bellamy et al. 1988), SF36 is a generic health measure (Ware and Sherbourne1992). The Oxford Knee Score, OKS is a knee scoring system which was specifically developed for total

knee arthroplasty patients and is also in wide use, especially in the U.K. (Dawson et al. 1998).

Details of the psychometric properties of WOMAC, SF-36 and OKS are as shown in Table 1.

Oxford Knee Score (OKS)

The OKS questionnaire was developed by the authors using patient inputs in order to make the questionnaire as valid and sensitive as possible (Dawson et al. 1998). It has been tested by its authors for internal consistency (Cronbachs alpha = 0.87-0.93), test retest reliability (r= 0.92), construct validity and sensitivity to change with KSS, SF36 and Health Assessment Questionnaire (HAQ) (Dawson et al. 1998). The Oxford Knee Score is an attempt to create an assessment tool specific to the total knee replacement. Its short and simplified form allows for patient compliance and is currently the most preferred method of assessment by the active members of the British Association of Surgery of Knee (Davies 2002).

Short Form -12 Health Survey (SF-12)

With the recognition that a comprehensive assessment of outcomes of care goes beyond the traditional clinical view to also include the patients overall health and general wellbeing, a number of questionnaires have been developed to assess dimensions covering physical, psychological and social function. As mentioned earlier, the Short Form 36 (SF36) is one of the most widely used generic outcome measures for TKA patients. It has shown suitability in terms of validity and internal consistency as an outcome measure for routine use within the NHS for some common clinical conditions (Garrat et al. 1993). The Short From -12 (SF12) questionnaire was derived from the SF36 in an attempt to create a shorter version of the SF36 scale (Ware et al. 1996). Based on the findings that the physical and mental health factors account for 80-85% of the reliability variance in the eight scales of SF36 and that the Physical Component Summary

(PCS) and Mental Component Summary (MCS) detected the hypothesized differences in nearly all test using physical criteria and mental criteria respectively; the authors saw it possible to reduce the number of health dimensions into PCS and MCS without substantial loss of information (Ware et al. 1996). This adaptation of the SF36 into SF12 showed a close and linear relation with the SF-36 while its brevity added to patient compliance (Wareet al. 1996).

The current thesis uses a combination of a joint/disease specific outcomes measure and a generic health outcomes measure through the OKS and SF12 questionnaires. A disease specific questionnaire is more responsive in the evaluation of a particular condition (Brazier et al. 1999). Also, considering that functional ability, especially in the elderly is influenced by factors not related to the joint such as comorbidity and psychosocial factors, the generic health instruments adds to the evaluation in the dimensions of physical , psychological and social function. Furthermore, OKS and SF12 are instruments that are routinely used for TKA patients within the NHS Lothian allowing for comparison between the results of the retrospective and prospective studies of the thesis.

Table 1 Psychometric properties and applicability of outcomes questionnaires used commonly for TKA patients

Outcome measure	Measurement	Validity	Reliability	Responsiveness	Applicability
HSS (Insall 1976)	Pain, function, range of motion, muscle strength, flexion deformity, instability, deduction for walking aid, extension lag and varus/valgus.	Well correlated with kinesiologic measurement of post-operative function, prosthetic alignment thus valid (Gore et al. 1986)	Good inter-observer reliability, r=0.82 (Bach et al. (2002)		Easy to use and widely followed. However, was developed when TKA was at its infancy and the expectations of outcomes were less (Insall et al. 1989)
KSS (Insall 1989)	Knee score (pain, range of motion, stability, and alignment, deduction for flexion contracture and extension lag). Function (walking, stair climbing, deduction for walking aid).	Validated against WOMAC and SF36. Good convergent construct validity between knee score and WOMAC pain score, r=0.68. and KSS function score SF36(PC), r=0.72; 12 month post op (Lingard et al.2001), correlation between items poor.	Knee score has poor inter-observer reproducibility (r= 0.48). Good inter-observer reproducibility in case of function score, r=0.78. (Bach et al. 2002)	KSS knee score and WOMAC pain score more responsive than SF36 pain score. KSS less responsive than WOMAC and SF36 for patient perceived outcomes (Lingard et al 2001) More responsive than SF36, walk test, stair test, time trade off (Kreibich et al. 1996)	Clearly separates knee function from overall physical function. Concise and easy to use and currently most widely used in the U.K. Also, most used in related research (Davis 2002)

Outcome measure	Measurement	Validity	Reliability	Responsiveness	Applicability
WOMAC Bellamy et al. (1988)	Three components: Pain, stiffness, function. Self-reported	Validated for measuring outcomes post TKA by Bellamy et al. (1988)	Self-reported measure thus removes observer bias	More responsive than the KSS (Lingard et al. 2001). More responsive than SF36, walk test, stair test, time trade off(Kreibich et al. 1996)	Self-report measure thus less labour intensive. However, response from subject is an influencing factor.
SF36 (Ware and Sherbourne 1992;	Functional status (physical function, social function, physical role function, emotional role function); Wellbeing (mental health, energy, pain) and General health perception. Self-reported	Well validated and tested for reliability (Ware and Sherbourne 1992;McHorney, et al.1993). Valid and internally consistent for patient outcomes NHS (Garrat et al. 1993)	Self-reported measure thus removes observer bias. Good test retest reliability, r = 0.85 (Beaton et al. 1997)	Most responsive among NHP, OHS, Duke health profile and Sickness impact profile in subjects with musculoskeletal disorders (Beaton et al. 1997)	Self-report measure thus lesslabour intensive. However, it is a generic measure and not specific to knee thus sections such as pain assessment might not be as responsive as KSS/WOMAC.
Oxford Knee Score (Dawson et al. 1998)	12 questions on patient's perception of pain and function. Self-reported.	Validated against KSS and SF36 (Dawson et al. 1998)	Self-reported measure thus no observer bias.	Test retest reliability good, r=0.92 (Dawson et al. 1998)	Self-reported thus less labour intensive. On comparison with WOMAC, it is more specifically for knee surgery and simpler to process. Though it may be widely used clinically in the U.K. related researches seem to make more use of the WOMAC.

2.6. Chapter summary

Total knee arthroplasty has been known to be a safe and effective orthopaedic procedure for the treatment of end-stage osteoarthritis. Advances in the procedure and availability have led to its wide utilization. Although a TKA cannot restore the joint function to normal, it offers considerable relief from pain and restoration of function. There are various approaches to measuring outcomes after TKA including a variety of scoring systems used measured by an examiner and those measured by patients themselves. Among the patient reported outcomes, WOMAC and SF36 have been most widely used in TKA patients. The studies in the current thesis have assessed outcomes after TKA using a combination of knee specific (OKS) and generic (SF12) patient reported outcomes to allow for responsiveness to the functional changes particular to the joint as well as take into consideration the physical, psychological and social dimensions which affect the overall functional ability.

CHAPTER 3: OBESITY

3.1. Chapter overview

This chapter presents an overview of the prevalence of obesity in the general population and TKA population. The effect of obesity on an osteoarthritic joint is then discussed followed by a brief discussion of methods of measuring body composition.

3.2. Obesity: Overview and prevalence in the general population

Obesity has been defined as the accumulation of excessive body fat to the extent that it may have a detrimental effect on health (World Health Organization, WHO 2000). Body mass index (BMI) is widely used in clinical settings and population studies to measure obesity. With a reasonable correlation with body fat mass and obesity associated health risks, BMI is a useful measure to estimate the prevalence of obesity at population level (Canyon and Buchan 2007). According to the WHO classification of obesity, a BMI between 25 to 29.9 kg/m^2 is considered overweight while a BMI greater than 29.9 kg/m^2 is considered obese.

The WHO report (2000) describes obesity as the most common nutritional disorder which is increasing at an alarming rate in both developed and developing countries. A steady rise in the prevalence of obesity has been reported in Scotland since 1995. In Scotland, among men aged 16-64 years, the prevalence rose from 15.9% in 1995 to 26.6 % in 2010. For females of the same age range the figures rose from 17.3% in 1995 28.1% in 2010 (Scottish Health Survey 2010). The figures for obesity prevalence in 2009 and 2010 were

similar but it has been suggested that this might not necessarily mean that the increase over time has started to plateau and that only once further prevalence data for 2011 and onwards, it can be known if the rise is continued or stabilized (Scottish Health Survey 2010). In England, according to the Health Survey for England report (2010), the obesity prevalence in England have risen from 13% in 1993 to 26% in 2010 for men and correspondingly from 16% to 26% for women. The survey also illustrate that obesity tends to increase with age and regional differences are seen with the prevalence of obesity greater in North England and Scotland (Rennie and Jebb 2005).

3.3. Prevalence of obesity in the TKA population

The above health survey reports have reported that obesity increases with age and declines from the 7th decade of life. Flegal et al. (2002) in their survey in America observed that the peak incidence of obesity occurred in the 6th decade. A similar trend was seen in the Scottish Health survey with highest incidences of obesity in the age rages 55-64 years (38.3% in this age group were obese in 2010) and 65- 74 years (33% obese in this age range in 2010). This also coincides with the age range for primary total knee arthroplasty in Scotland for year 2009 when a median of 69 years and inter quartile range of 62-75 years was reported (Scottish Arthroplasty Project report 2010). Thus with the increasing obesity and aging population, it seems likely that a considerable proportion of patients undergoing total knee arthroplasty will be in the obese category.

3.4. Obesity and its effect on knee osteoarthritis

A strong positive association of obesity and knee osteoarthritis has long been established by several studies including cohort studies, cross sectional studies and case control studies (Felson et al. 1988, Hartz et al. 1986, Sturmer et al. 2000). One of the key studies in this area, the Farmingham study by Felson et al. (1988), in a cohort of 1450 individuals, saw a strong and consistent association of obesity and overweight with the onset of knee osteoarthritis. Overweight and obesity in this study were defined as the heaviest and the second heaviest quintiles of the Metropolitan Relative Weight[1]. The study found that increasing weight was associated with greater risk of both symptomatic and asymptomatic, radiographic knee osteoarthritis (relative risk = 1.54, 95% CI = 1.18-2.02 for men) and this association were persistent after controlling for age, uric acid levels and physical activity levels. Also, the association between obesity and knee osteoarthritis was seen to be stronger for women (relative risk = 1.93, 95% CI = 1.56-2.37). Assessment of knee osteoarthritis at follow up (34 years) after baseline measurements of weight, allows this study to address the time sequence between obesity and development of knee osteoarthritis as opposed to cross sectional studies such as that by Strummer et al. (2000) as OA could lead to a sedentary life and consequently obesity.

It is proposed that the link between obesity and knee osteoarthritis is because of the increased forces on the cartilage due to the additional weight. Also, obesity causes subchondral bone stiffness such that the bone is not deformable to impact loads and transmits greater forces than normal to the overlying cartilage thus rendering the cartilage vulnerable to degeneration (Felson et al. 1988;Hills et al. 2002; Marks 2007,). Messier et al. (1994) analyzed the effect of knee OA on gait and observed a transient peak in the ground reaction force data symbolizing an increased force on heel impact, in obese patients. They conclude that a shorter period of eccentric quadriceps muscle action at heel strike results in decreased shock absorption. Decrease shock absorption and repeated impulse loading results in stiffening of the bone due to the healing of micro fractures. The notion that obesity increases the loading at the joint though seems like an obvious one, it does not answer why all obese persons do not have OA and how these individuals

compensate for increased load on their knee joint. Devita and Hortobagyi. (2003) on comparing the knee kinetics during walking between lean individuals and obese but otherwise healthy individuals found that the knee torque and power in obese was lower when walking at their self-selected pace and equal torque and power when walking in the same speed as the lean individuals. Therefore they proposed that ability to reorganize neuromuscular function so as to produce a gait pattern which induces lesser load on the joint allows some obese individuals to maintain the integrity of the knee joint. On the other hand, in other obese individuals, the biomechanical loading of the knee joint due to excess weight represents a possible pathway for the pathogenesis of OA (Messier et al. 2005). In obese individuals with OA, Messier et al. (2005) saw a significant relationship between weight loss and decrease in compressive knee joint forces such that with every unit of reduction in weight, there was a four unit reduction in the compressive joint forces at the knee.

The increased compressive forces at the knee joint due to excess weight implies that the same association must be true for all other weight bearing joints in obese persons, such as, the hip. However, the association of obesity with hip OA is not as strong as that with knee osteoarthritis. The association of obesity with radiographic hip osteoarthritis is unclear as some studies find a significant association with hip OA (Oliveria et al. 1999; Jarvholm et al. 2005) and while others have found no significant association between obesity and hip OA (Reijman et al. 2006; Grotle et al. 2008). In a systematic review of the influence of obesity on the development of hip osteoarthritis, moderate evidence was found for a positive association of obesity with hip osteoarthritis with an odds ratio of approximately two (Lievense et al. 2002). It is suggested that a lack of association between increased weight and hip OA may be evidence for the differential effects of increased load of knee and hip joints. Reijman et al. (2006) suggest that while malalignment is not a problem per definition in a ball and socket joint like the hip, it is a problem in a hinge joint like the knee. Since it is reported that the effect of obesity is modified by malalignment of the joint (Felson et al. . 2004), Reijman et al. (2006) further suggest that the higher stresses caused by obesity are compounded in a malaligned hinge joint owing to the smaller area for the forces to act upon. Sturmer et al. (2000) further hypothesize that the distribution of body fat might also explain the observed difference in

the link between obesity and bilateral OA of the hip and knee, such that, while fat at the waist is supported by both hip and knee, the thigh and hip fat have less influence on the compressive stresses at the hip.

The effect of obesity on onset of OA due increase in the compressive forces in the joints is further confounded by the association seen between obesity and hand OA. A recent systematic review (Yusuf et al. 2010), of the 15 studies that were considered high quality studies, 10 studies pointed to a positive association between BMI and hand OA. This indicates that factors other than mechanical effects of obesity play a role in the development of osteoarthritis. It is suggested that these patterns of joint involvement in osteoarthritis may be caused by systemic factors such as the adipokines released by fat tissues thus providing a metabolic link between obesity and osteoarthritis. Adipokines such as leptins secreted by adipose tissues have been observed in the synovial fluid of osteoarthritic joint. Moreover, the level and pattern of expression of leptins have been correlated with both BMI and the grade of cartilage destruction (Dumond et al. 2003). From these findings, it is hypothesized that the dysregulation of lipid haemostasis can be one of the pathological mechanisms causing osteoarthritis (Pottie et al. 2006).

The association of obesity with onset of knee OA is seen to be stronger in females than in males (Felson 1988; Sturmer 2000). While no link between estrogen use in women and osteoarthritis have yet been found, it has been hypothesized that differences in the body composition of males and females may have a role in determining the association of obesity with osteoarthritis (Hills et al. 2002). At identical heights, an average female has 8-10% higher body fat and lower muscle mass than an average male (Syed and Davis 2000). The lower proportion of muscle mass may mean lesser musculoskeletal support and decreased ability for shock absorption at the joint for females thus predisposing the knee joint to greater forces and an increased degeneration of the cartilage (Syed and Davis 2000; Hills et al. 2002).

The reduction in lean mass and increase in body fat is also a function of aging. The reduction in lean mass is possibly parallel with the reduction in muscle mass, muscle strength and functional capacity (Messier et al. 1994). The decrease in the muscle strength of key leg muscles such as quadriceps may lead to a reduced period of

quadriceps eccentric activity at heel strike as mentioned above (Messier et al. 1994). Syed and Davis (2000) suggest a combination of early muscle fatigue due to weakness and increase in ground reaction forces in obese result in the higher loading detrimental to the knee.

In the study of association of obesity as a significant risk factor for osteoarthritis, obesity has been usually characterized by BMI. As BMI is a measure of combined fat and lean mass, it does not distinguish between the relative contribution of the adipose tissue and muscle mass towards the mechanisms leading to the development of OA. Various studies have assessed the association of other measures of body composition with the development of osteoarthritis. However, the evidence is conflicting with regards to independent effects of these measures. Hart and Spector (1993) observed that body fat distribution measures such a waist, hip and thigh circumferences did not have a greater predictive ability over BMI for the development of osteoarthritis. Similarly, Hochberg et al. (1995) observed that body fat percentage and waist to hip ratio had no significant association with knee OA after adjusting for BMI. These studies suggest that the influence of obesity on the development of knee osteoarthritis is primarily through increased mechanical loading due to increased mass than through systemic or metabolic effects of adiposity. Using Dual-energy X-ray absorptiometry (DXA) scan to produce total body fat mass, lean mass and bone mass, Abbate et al. (2006) found that neither these parameters nor waist to hip ratio offered any advantage over BMI in predicting knee osteoarthritis. Sowers et al. (2008) on the other hand observed that statistical models that included age and body composition (differentiated as fat mass and skeletal muscle mass) had a better statistical fit than BMI in order to explain the odds of onset of knee OA and its severity. Sowers et al. (2008) propose that the difference in their finding was due to the evaluation of lean mass (comprising muscle, bone, intracellular and extracellular fluids) by Abate et al. (2006) as opposed to the muscle mass. Two recent and largest prospective cohort studies (Lohmander et al. 2009 and Wang et al. 2009) assessed the association of various overweight and obesity measure on the risk of severe knee osteoarthritis (defined as risk of a knee arthroplasty) and found an association between various obesity measures and the risk of knee arthroplasty. Lohmander et al. (2009) observed that there was a BMI, weight and waist circumference were significantly

associated with knee osteoarthritis with relative risk (95% CI) of 8.1(5.3 to 12.4) for BMI, 6.7 (4.5 to 9.9) for waist circumference, 6.5 (4.6 to 9.43) for weight but body fat percentage (BF%) and waist to hip ratio (WHR) was only weakly associated with knee osteoarthritis (relative risk [95% CI] = 3.6 [2.6 to 5.0] for BF% and 2.2 [1.7 to 3.0] for WHR). Wang et al. 2009 saw a three to four fold increase in the risk of primary total knee replacement when comparing the first and the fourth quintiles of BMI, weight, fat mass and fat percentage. The waist circumference and the waist to hip ratio, however, had a weaker association with the risk. Therefore, with the association of BMI, adipose distribution and adipose mass with the risk of knee arthroplasty, these studies concluded that both mechanical and metabolic effect of obesity play a role in the development of osteoarthritis.

3.4.1. Section summary

Though a positive association of obesity with the development of osteoarthritis has been established, the importance of understanding the mechanism by which obesity affects the joint in the prevention and treatment of OA has been recognized. The most obvious mechanism through which obesity predisposes OA is proposed to be the mechanical effect of the increased load on the joint and the resultant cartilage degeneration. However, the differential effect of higher mass on other weight bearing joints, association of obesity with non-weight bearing joints, the fact that not all obese persons are affected by osteoarthritis and the greater association of obesity with knee osteoarthritis in women than men indicates towards mechanisms other than just the mechanical effect of a greater mass. The literature assessing the association of various measures of obesity and overweight with knee OA shows inconsistencies. These could be a resultant of the different categorization of the measures used in studies. Also, the studies vary in defining knee osteoarthritis radiograhically, symptomatically or as patients who have been recommended a knee arthroplasty.

3.5. Measurement of obesity

Details of validity and applicability of various body composition measures have been listed in Table 2.

The most widely used measures of obesity both in practice and in research are the anthropometric measures such as BMI, waist circumference, waist to hip ratio and skin fold thickness measurement. While BMI measures total body mass, waist circumference and waist to hip ratio are used to estimate abdominal obesity and fat distribution. The simplicity of use of these anthropometric measures and their association with health risks enable them to be widely used in large population studies and are reported as estimates of obesity in health reports (WHO 1995, Scottish Health Survey 2010, Health Survey for England 2010). Anthropometric measure used to estimate subcutaneous fat thickness is the skinfold measurement. Subcutaneous fat thickness is now also measured using the ultrasound technique. Though more difficult to use and more expensive than skinfold measure the ultrasonography technique offers the advantage of avoiding tissue compression, no requirement for palpation of muscle tissue interface and valid measurements in obese subjects compared to skinfold measure (Selkow et al. 2011).

No particular method of body composition is considered as the best or 'gold standard'. Methods like Computerised Tomography Scan (CT scan), Magnetic Resonance Imaging (MRI), hydrodensitometry show high levels of accuracy in measuring fat mass (Table 2) (Rossner et al.; 1990; Abate et al. 1994; Mitsiopoulos et al.1998; Ginde et al. 2005). However, the application of these methods in clinical and research settings is limited by cost and labour implication in addition to safety issues such as exposure to radiation. Less expensive and elaborate measurement methods which are fairly accurate, are the air displacement plethysmography and the dual X ray absorptiometry (DXA) (Snijder et al. 2002; Ginde et al. 2005; Noreen and Lemon 2006; Anderson 2007; Hill et al. 2007). However, these still involve considerable cost and specialist skill for use in the clinical setting. Dual X ray absorptiometry is relatively cheaper than the above methods and has been well validated against CT scan. It has also shown to have high inter-tester reliability

(r = 0.99) (Snijder et al. 2002; Hill et al. 2007). However, the weight limit of the DXA compartment and limited portability makes its use difficult especially where heavy post-operative patients are concerned. Among the more clinically viable methods of measurement of body composition, the bioelectrical impedance analyzers measure the total body water from which fat mass and lean mass is estimated. The method is noninvasive, cost effective and portable and therefore an attractive alternative for clinical or field application (Kyle et al.2004)

The assessment of the effect of obesity and osteoarthritis has been primarily done by employing obesity measures of weight and BMI. Later studies have also linked waist circumference, waist to hip ratio and body fat percentage in the association of obesity and osteoarthritis. For TKA patients, the effect of obesity on outcomes have todate been measured by weight and BMI. The following chapters of the thesis aim to present the findings of the effect of obesity on TKA outcomes with obesity measured as BMI; and also assess the effect of obesity as measured by a range of body composition measures including waist circumference, waist to hip ratio, bioelectrical impedance analysis and ultrasonography in addition to BMI on outcomes following TKA.

Table 2 Body composition measurement methods: validity and applicability

Measurement Technique	**Accuracy /validation**	**Applicability**
CT scan	High Validated against cadaver study (Mitsipoulos et al. 1998 r = 0.99); and cross sectional planimetry in cadavers(Rossner 1990 r = 0.99)	Difficult Cost Exposure to radiations
MRI	High Validated against cadaver study (Mitsiopoulos et al. 1998 r = 0.99; Abate et al., 1994 diff = 0.076kg) Inter-observer reliability good, r = 0.99 (Mitsiopoulos et al. 1998)	Difficult Cost
Hydrostatic weighing (HW) Measures body volume from which body fat is determined	High Considered 'gold standard' for measuring body volume and thus used as reference method for validating other method (Ginde et al. 2005)	Difficult Cost and labour intensive Patient discomfort and apprehension Safety issues Time consuming
Air displacement plethysmography Measures body volume from which body fat is determined	High Validated against hydrostatic weighing (Ginde et al. 2005, r = 0.94) Test retest reliability good r = 0.99 (Noreen and Lemon, 2006) Contrary, within day reliability good r= 0.98 but significant differences between different day measures (Anderson 2007)	Difficult More suitable alternative to HW. Suitable for very heavy patients Cost and specialist skill required
DEXA Measures bone mineral density, fat mass and soft tissue mass.	High Validated against CT scan for determining total abdominal fat, r = 0.87 to 0.98 (Snijder et al. 2002) High inter tester reliability for fat mass (r = 0.99) and lean mass (r = 0.98) (Hill et al. 2007)	Moderate Cost Severely obese may exceed the weight limit of the compartment

Ultrasound	Moderate Validated against CT scan for abdominal adipose r = 0.81 (Stolk et al. 2001), and total fat r = 0.75 (Ribeiro-Filho et al. 2003) Some studies show poor reliability, however, Stolk et al. (2001) show good reliability with a strict protocol, r = 0.94	Moderate Portable Skill required
BIA Measures electrical resistance offered by body, thus estimates TBW which is used to calculate fat free mass and fat mass.	High Hand held BIA validated against DEXA r = 0.87(men); r = 0.83 (women) (Deurenberg et al. 2001)	Easy Not expensive Portable Hydration condition should be maintained for accurate measurement
Skin fold measurement Skinfold thickness measured using callipers	Low Five currently used equations validated against HW in children showed large errors. Thus suggested that it can be useful as an indices and not a measure (Reilly et al. 1995) Results affected by inter-observer errors, choice of calipers, selection of skinfold sites (Pollock et al. 1988)	Easy Simple and quick Minimum labour and cost
BMI Calculated as weight (in kilograms) divided by square of height in meters	Moderate Can be used as baseline data or longitudinal measure to determine relative body weight. Does not differentiate fat and fat free mass thus accuracy in determining total body fat doubtful (Wells and Fewtrell 2006)	Easy Simple and quick Reliable
Waist circumference Used as an indicator of abdominal fat	Moderate Validation against MRI for abdominal fat (r = 0.4-0.8).Waist to hip ratio showed inconsistent or no significant relation to abdominal fat (r = 0.4-0.7) (Chan et al. 2003)	Easy Simple and quick Reliable

CHAPTER 4: EFFECT OF BMI ON OUTCOMES FOLLOWING TKA- LITERATURE REVIEW

4.1. Chapter overview

This chapter presents the literature review used to evaluate the effect of obesity (defined by BMI) on outcomes following TKA. After a brief background to the literature review; previous evidence of the effect of BMI on post-operative complications, questionnaire based functional outcomes and prosthetic longevity is discussed. This is followed by a discussion of the other factors associated with obesity which may influence the outcomes. Finally, a summary of the conclusions from the evidence is presented.

4.2. Introduction and background

It is seen that the proportion of patients with higher body mass index (BMI) undergoing total knee arthroplasty (TKA) is much higher than that of patients with lower BMI (Bostman 1994; Fehring et al. 2007). Moreover, this trend of higher proportion of patients with greater body mass among the total knee arthroplasty population shows an increase over the years (Fehring et al. 2007).

The influence of obesity on knee osteoarthritis implies that with increasing obesity and aging of the population, the proportion of obese osteoarthritis patients undergoing total knee replacement is on the rise and is likely to reach higher levels in future.

These increasing trends in the prevalence of obesity in TKA population have led to concerns regarding the outcomes of the surgery in obese patients. Obesity is considered

as a risk factor for a number of surgical complications and despite advancements and improvement in alignment and insertion techniques, there also remain concerns about the impact of the added stress on the underlying bone and implant material in obese patients thereby affecting the prosthetic longevity and functional gain (Winiarsky et al. 1998, Miric et al. 2002, Namba et al. 2005).

In addition to concerns over the increased rates of peri-operative complications, increased stress on the implanted prosthesis and thus the success of surgery in this patient group, there are implications of increased financial burden on health care services in managing these complications. In response to a perceived increased risk and cost of the procedure in these patients, three primary care trusts recently followed the 'Ipswich protocol' which restricted access to TKA in patients with BMI $\geq$ 30 kg/m^2(Gillespie and Porteous 2007). This prioritization in favor of non-obese has been the topic of much controversy since there is little agreement over predilection for adverse outcomes in the obese TKA population. Several studies report no significant differences in the outcomes in obese and non-obese patients (Jiganti et al. 1993; Spicer et al., 2001; Stickles et al., 2001; Deshmukh et al., 2002; Amin et al. 2006a) and on the other hand, some studies find obese patients with inferior outcomes in terms of post-operative complications, function and revision rates (Winiarsky, et al.1998; Griffin et al., 1998; Miric et al., 2002; Foran et al., 2004; Namba et al., 2005; Jackson et al 2009; Dowsey et al. 2010).

Thus as the prevalence of obesity and aging of the population continues to rise, it is important to define the relationship between obesity and the outcomes of TKA. From the demographics of obesity in the U.K it is clear that in regions like Scotland, the prevalence of obesity is high and indeed higher than the U.K average prevalence thus making it important for assessing the influence of obesity on TKA outcomes especially in this region.

4.3. Obesity and post-operative complications post TKA

Obesity, defined by BMI has been identified as an independent risk factor for post-operative complication in patients undergoing lower limb arthroplasty by some studies (Jain et al. 2005; Parvizi et al. 2007). Based on a nationwide inpatient care database investigating approximately one million patients in the U.S.A, the study by Jain et al. (2005) showed that the risk of postoperative complications after major joint arthroplasty (shoulder, hip and knee) was 1.3 times more likely in obese.patients

Specific to the TKA population, two earlier studies investigating the link between obesity and post-operative complications have defined obesity in terms of ideal body weight derived from insurance company statistics (Stern and Insall 1990 and Jiganti et al. 1993). In a retrospective review comparing 51 non-obese TKA patients with 103 obese TKA patients by Jiganti et al. (1993), there was no association between obesity and peri-operative morbidity. These findings were concurrent with that from the study by Stern and Insall (1990). Though not statistically significant, Jiganti et al. (1993) in fact saw a lower rate of major and minor complications in obese patients. Although, it has been noted, that on the comparison of sample characteristics of the obese and non-obese groups in this study, pre-existing medical conditions and rheumatoid arthritis were higher in their non-obese group (30% in non-obese patients vs. 14% in obese patients).

The most common definition of obesity that is currently used is the Body Mass Index (BMI) and has been used to define obesity in most of the papers under review. BMI is also known as the Quetlet Index and is calculated as the ratio of the body weight in kilograms to the square of height in meters. Using BMI, obesity is then defined as BMI equal to or greater than 30 kg/m². A more detailed classification of BMI suggests division into five groups of BMI, these being BMI < 25 kg/m^2 (healthy); BMI = 25-29.9 kg/m^2 (overweight); BMI = 30-34.9 kg/m^2 (class I obese); BMI = 35-39.9 kg/m^2 (class II obese) ; BMI $\geq$ 40 kg/m^2 (class III obese) (WHO 2000)

4.3.1. Comparison between obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2) patients

In a prospective study comparing 210 TKA in non-obese with 160 TKA in patients with obesity, there was no difference across the two BMI groups (non-obese patients with BMI<30 kg/m² and obese patients with BMI ≥30 kg/m²) for superficial wound infection, deep joint infection, deep vein thrombosis (DVT), pulmonary embolism and peri-operative mortality (Amin et al. 2006a).On the other hand, a study by Dowsey et al. (2010), saw significantly higher rates prosthetic infection, superficial wound complication and deep vein thrombosis (DVT) in their 261 obese patients (BMI = 30-39 kg/m²) than in their 211 non-obese (BMI < 30 kg/m²) TKA patients. An overall complications rate of 3% (a DVT, wound dehiscence and a foot drop) was seen in 78 obese TKA patients compared to 0% in 78 non-obese TKA patients in a retrospective matched study (Foran et al. 2004b). This higher rate of complication in obese patients however, did not reach statistical significance in this study.

4.3.2. Comparison between obese (BMI ≥35) and non-obese (BMI <35) patients

While the above studies grouped obese and non-obese based on BMI a cut off value of 30 kg/m², Miric et al. (2002) in a prospective review divided obese and non-obese groups based on BMI greater or less than 35 kg/m². They found a significantly increased incidence of post-operative complications in obese TKA patients (n = 86) i.e., the number of patients who had a complication or multiple complications was higher in patients with a BMI ≥ 35 kg/m² compared to non-obese TKA patients with BMI < 35 kg/m² (n = 320). Of the patients with BMI ≥ 35 kg/m², 38% experienced a complication, whereas only 25% of patients with BMI < 35 kg/m²experienced some type of peri-operative complication. In this study complications were defined as ‘any problem that required additional therapeutic intervention’ and individual complications categorized according to the body system affected were not analyzed separately. Also, in contrast to Jiganti et al. (1993), who observed greater number of comorbidity in their non-obese group, a higher rate of significant preexisting medical condition (cardiac and diabetes mellitus)

was seen in the group of patients with higher BMI in this study. Another study found a higher rate of post-operative infection in patients with BMI ≥ 35 kg/m² but saw a similar distribution of other medical complications like DVT, cardiac, gastro intestinal and pulmonary complications between their obese and non-obese groups (Namba et al. 2005). A case control study with 12 month follow up (Nunez et al. 2010), reported greater intra operative difficulties and more severe complications in their obese group (BMI ≥ 35 kg/m^2) which included deep infection, loosening of tibial implant, re intervention for patellar prosthesis and re intervention for arthrolysis due to stiffness compared to the matched control group (BMI <35 kg/m^2, matched for age, sex and pre-operative WOMAC score). In contrast to these findings, Stickles et al. (2001) saw no difference in the complication rates between obese and non-obese and even across their five BMI groups (grouping as described above).

4.3.3. Post-operative complications in the morbidly obese (BMI ≥ 40kg/m^2)

Significantly higher rates of wound complication, infections, prosthetic failure and intra operative avulsion of medial collateral ligament have reported in the morbidly obese by Winiarsky et al. (1998). Similarly, Amin et al. (2006b) saw a higher rate of these complications in their morbidly obese groups. However, there was no intra operative avulsion of the medial collateral ligament in the morbidly obese group as that reported by Winiarsky et al. (1998). Krushell and Fingeroth (2007), in a retrospective examination of 39 TKA in patients with BMI ≥40 kg/m^2 vs. 39 controls with BMI < 30 kg/m^2, also saw a significantly higher rate of early wound complications in their morbidly obese group. Thus, the evidence above does indicate that the risk of post-operative infection increases after a BMI of 40 kg/m^2.Thelatter two studies have compared morbidly obese (BMI ≥40 kg/m^2) with the non-obese patients (BMI <30 kg/m^2). On comparing patients with BMI greater than 40 kg/m^2 and patients with a BMI < 40 kg/m^2, similar to Winiarsky et al. (1998), Maliznak et al. (2009) reported a 3.2 times odds of infection in patient ($p < 0.05$).

4.3.4. BMI and post-operative complications: Summary

The relationship between obesity and the rates of post-operative complications following a TKA is not very clear from the literature. One of the difficulties in comparing the literature is the use of different measures to define obesity. Earlier studies have defined obesity as 20% above the ideal body weight based on 1983 Metropolitan life insurance company statistics (Stern and Insall 1990; Jigati et al. 1993). Later studies and in fact most studies till now have defined obesity in terms of BMI. Body mass index by these authors is considered a more established measure of obesity which has a better correlation with body fat compared to measures purely based on weight. On comparison of studies which have used BMI to define obesity for assessment of post-operative complication rates, the results still appear conflicting. While Miric et al. (2002), Namba et al. (2005), Nunez et al. (2010) and Dowsey et al. (2010) reported some association between BMI and post-operative complications, Amin et al. (2006a), Stickles et al (2001)reported no differences across the BMI groups. The division of patients into 'obese' and 'non-obese' groups was also different in the studies. Body mass index cut off value defining obesity was 30 kg/m^2 in some studies, 35 kg/m^2 in others while the study by Stickles et al. (2001) divided the patients into five BMI groups (< 25 kg/m^2, healthy; 25-29.9 kg/m^2, overweight; 30-34.9 $kg.m^2$, class I obese, 35-39.9 kg/m^2, class II obese; $\geq$ 40 kg/m^2, class III obese). Some consistency was seen in the reports showing an increased risk of infection in BMI greater than 35 kg/m^2 and more so in studies comparing morbidly obese (BMI $\geq$ 40 kg/m^2) with BMI < 30 kg/m^2 (Amin et al. 2006b; Krushell and Fingeroth 2007) or BMI < 40kg/m^2

Another difficulty in comparison between literatures is due to the different approaches by authors towards defining and classifying post-operative complications. While Stern and Insall (1990) have recorded data on relatively few complications (thrombophlebitis and wound complications), Miric et al. (2002) have considered a more comprehensive list of complications classifying them according to the site of affection. The focus of most studies is on post-operative rates of infection and wound complications. Differences further exist in approaches towards defining wound complication and infection. For example, Namba et al. (2005) reported an odds ratio of 6.7 times higher risk of infection

in highly obese TKA patients (BMI ≥35 kg/m^2). This study described superficial infection as those cases requiring intravenous antibiotics while those treated operatively or any positive culture were considered as deep infection. They did not record superficial cellulitis managed with oral antibiotics as an infection. On the other hand, Krushell and Fingeroth (2007) who also reported a significantly higher rate of post-operative infection in their morbidly obese group (BMI ≥40 kg/m^2) did however, record superficial cellulitis treated with oral antibiotics as a wound complication.

There are several factors apart from BMI which may lead to an incident of post-operative complication in TKA patients such as other comorbidity. As described in the above section, conflicting results were seen in the studies by Miric et al. (2002) and Jiganti et al. (1993), where Miric et al. (2002) saw a higher rate of post-operative complications in obese while Jiganti et al. (1993) saw a lower rate of post-operative complications in the obese. On observing the preexisting medical condition in the groups, it was noted that these were higher in the obese group in the study by Miric et al. (2002) and were observed higher in the non-obese groups by Jiganti et al. (1993). This indicated that in these samples, there is some influence of the preexisting medical comorbidity on the groups.

The conflicting results and the different stratification of obese and non-obese therefore makes it difficult to conclude about a specific cut off point of BMI above which predisposes a higher risk of post-operative complication. Grouping patients into obese and non-obese based on BMI greater or less than 30 kg/m^2 seem to show conflicting results with respect to rates of post-operative infection and DVT between obese and non-obese. However, there seems to be an association of risk of post-operative complication with increasing obesity such that the results of the studies comparing morbidly obese patients with BMI ≥ 40 kg/m^2 with non-obese patients having BMI < 30 kg/m^2 are more concurrent with each other indicating a higher risk of post-operative complication, in particular infection, in the patients with BMI ≥ 40 kg/m^2. Some evidence of the higher incidence of post-operative complications, though not consistent in studies, seen when classifying patients into highly obese i.e, those with a BMI ≥ 35 kg/$m^2$and non-obese (BMI < 35 kg/m^2) could be suggestive of a larger range of patients at an increased risk of

post-operative complication than that reported for morbidly obese patients. Group comparison between highly obese (BMI $\geq$ 35 kg/m^2) and morbidly obese (BMI $\geq$ 40 kg/m^2) have not been done separately. Among studies comparing three or five BMI, while Dowsey et al. (2010) (three BMI groups) reported higher prosthetic infection, DVT in patients with BMI = 30-39.9 and BMI $\geq$ 40 kg/m^2 compared to BMI <30 kg/m^2, Stickles et al. (2001) (five BMI groups) reported no difference in the complication rates between their five BMI groups.

4.4. Obesity and clinical outcomes scores

Various outcomes scoring systems specific to the knee joint and or assessing patient function have been used to compare the outcomes of TKA between obese and non-obese.

4.4.1. Comparison of Knee Society Score (KSS) between obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI <30 kg/m^2)

A commonly used scoring system in these studies is the Knee Society Score (KSS) (Table 3). This form of scoring system consists of two parts, one objectively evaluating the knee joint and the other evaluating the overall functional level of the patient (Insall et al. 1989). From the studies comparing the Knee Society Score for obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI <30 kg/m^2) at a follow up of ten years or more, Griffin et al. (1998) comparing 22 obese and 34 non-obese reported lower i.e., worse function part of the KSS in obese as compared to non-obese patients but saw similar knee scores of KSS between groups at a mean follow up of 10.6 years. The function score of KSS consists of two components of walking ability and stair climbing ability. The average score for walking ability in the obese patients in this study was comparable to that in non-obese but stair climbing ability was significantly lower in obese patient. This lowered the overall

KSS function score in obese patients compared to non-obese patients in this study. A study by Foran et al. (2004a) with a follow up of 15 years also saw significantly lower post-operative KSS scores in 27 obese patients compared to 27 matched non-obese patients at the last follow up. In the study by Griffin et al. (1998) KSS at baseline was not measured and therefore it is not known if the obese group in this study had baseline scores which could have influenced the poorer post-operative scores. On the other hand, the lack of difference in the baseline KSS scores between obese and non-obese in the Foran et al. (2004a) study indicates that lower pre baseline scores had little effect on the resulting poorer follow up scores in their obese group.

At a minimum follow up of five years, Foran et al. (2007b) in another study comparing outcomes in 78 obese patients (BMI $\geq$30 kg/m^2) with 78 matched controls (BMI <30 kg/m^2), reported no significant difference between the baseline KSS scores in obese and non-obese but again, the post-operative scores were significantly different between obese and non-obese (94 in obese versus 90 in non-obese for KSS knee score and 78 in obese vs. 71 in non-obese for KSS function score). Also, the improvement in scores (calculated as the difference between baseline and post-operative scores) in obese patients was significantly lower. In contrast to the above finding, several authors have not found significant differences in scores between obese and non-obese at an average follow up five years (Spicer et al. 2001; Amin et al. 2006a; Bourne et al. 2007; Dewan et al. 2009). No significant difference was found for post-operative KSS knee score at a five year follow up between 125 obese and 158 non-obese (84.1 in obese vs 85.4 in non-obese) by Amin et al. (2006). A separate analysis of patients with weight < 100 kg (n = 258) vs patients with weight $\geq$ 100 kg (n = 25) in this study did not show significant difference across any group at a five year follow up. Spicer et al. (2001) saw a lower baseline (pre-operative) KSS function score but comparable baseline KSS knee score in the 285 obese patients compared to 371 non-obese controls in their study. At a mean follow up of 6.3 years, the post-operative KSS score (knee or function) was not different across groups. Despite a lower KSS score in the baseline assessment, the improvement in scores which was calculated as the difference between baseline and post-operative score was not different between groups in this study which conflicts directly with the findings in the two studies by Foran et al. (Foran et al. 2004a and Foran et al. 2004b).

Assessing the influence of various patient factors (age, sex, diagnosis, BMI) on TKA outcomes with a follow up range of 5-11 years, Bourne et al. (2007) also concluded that BMI had little impact on the improvement of KSS scores from pre-operative state to post-operative state. In fact, Bourne et al. (2007) reported that the improvement in scores was greater for the obese; however, this did not reach a statistically significant level.

At a shorter follow up of one year, two studies in this review reported conflicting results. While Deshmukh et al. (2002) using hierarchical regression analysis reported that BMI did not account significantly for variation in one year post-operative KSS scores, the more recent study by Dowsey et al. (2010) observed a significantly lower one year post-operative KSS score in their obese (BMI $\geq$ 30 kg/m^2) and morbidly obese (BMI $\geq$ 40 kg/m^2) groups compared to the non-obese. In addition, they (Dowsey et al. 2010) reported lower improvement particularly in function and pain scores obese and morbidly obese

4.4.2. Comparison of Hospital for Special Surgery Score (HSS) between obese (BMI ≥ 30 kg/m^2) and non-obese (BMI <30 kg/m^2)

Two studies in the review compared HSS between obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) (Table 4). Griffin et al. (1998) at a ten year follow up reported similar scores between obese and non-obese even though the baseline HSS score for their obese group was lower. In contrast to this finding, Jackson et al. (2009) reported similar baseline scores between their obese and non-obese groups while lower follow up scores (average follow up of 9.2 years) in obese and also less improvement in obese at follow up compared to non-obese.

4.4.3. Comparison of WOMAC Score between obese and non-obese

WOMAC is a self-administered knee joint specific questionnaire. At a follow up of twelve months post-operatively, BMI did not affect total WOMAC scores (Stickles et al. 2001, Nunez et al. 2010). A worsening of reported function (decrease in total scores) as

BMI increased was observed by Stickles et al. (2001), but the change in the scores from baseline to one year was similar across their five BMI groups (Table 5). In the study by Nunez et al. (2010), BMI was categorized into severely obese (BMI $\geq$ 35 kg/m^2), and control (BMI < 35 kg/m^2). Even with a higher BMI cut off point of 35, the study saw similar WOMAC pre-operative and follow up scores between the groups (Effect sizes shown in Table 5). At a longer follow up for 5-11 years by Bourne et al. (2007), similar improvements in WOMAC scores were seen between their five BMI groups. Conclusions from these studies suggest that BMI groups are not significantly different in terms of self-report knee function as measured by WOMAC.

4.4.4. Comparison of SF36/SF12 scores between obese and non-obese

The overall health related quality of life measured by the Short Form 36 health survey (SF36) was seen to have a similar distribution by Stickles et al. (2001) i.e, the improvement of scores from pre-operative to post-operative follow up was similar in obese and non-obese groups. Similarly, BMI did not account for variation in SF36 at one month, three months or six months post-operatively as assessed by Stevens- Lapsley et al. (2009) (Table 6). Cushnaghan et al. (2008) compared SF36 scores in a patient group who had undergone TKA for osteoarthritis with a matched control group with knee osteoarthritis who had not previously undergone TKA. Comparison was done to assess the impact of factors like age, sex, comorbidity, BMI, baseline scores on TKA outcomes during a mean follow up period of 6.9 years. On analysis of 108 obese in patient group, it was shown that there was apparent improvement in both obese and non-obese in the patient group, though the improvement was less in obese compared to non-obese in this group (but not significantly lower). This study also compared obese TKA patients with obese controls with OA but no TKA and reported that there was a marked decline in physical function score of SF36 in obese controls. Therefore from this study it was concluded that adverse effects of high BMI with respect to physical function score of SF36 in obese patients is smaller compared to obese controls (without TKA) and not significant thus indicating a definite advantage of TKA in obese patients.

Two studies reviewed assessed Short Form 12 health survey (SF12) scores between obese and non-obese. Categorizing patients into five BMI groups, Bourne et al. (2007) saw similar improvements in SF12 scores between the BMI groups. However in contrast to this finding, Dowsey et al. (2010) reported poorer one year post-operative physical function of SF12 cores and lower improvement in SF12 scores in their obese and morbidly obese group.

4.4.5. Comparison of patient's satisfaction with surgery between obese and non-obese

Patient reported satisfaction levels were found to be similar between obese and non-obese groups by (Griffin et al. 1998; Stickles et al. 2001; Jackson et al. 2009).

However Namba et al. (2005) found a greater patient reported satisfaction in highly obese patients (patients with BMI $\geq$ 35 kg/m^2) when compared to non-obese patients. This result may be reflecting the greater improvement in reported pain in their highly obese group.

4.4.6. Outcomes scores in morbidly obese patients (BMI ≥40kg/m^2)

In studies primarily evaluating the TKA outcomes in morbidly obese patients (BMI $\geq$ 40 kg/m^2) , a significantly lower post-operative KSS score was seen in the morbidly obese group (Winiarsky et al. 1998; Amin et al. 2006b; Krushell and Fingeroth 2007) (Table 3). Although a significantly lower post-operative function score of KSS was seen, the knee score of KSS though lower in morbidly obese as compared to non-obese (85.7 vs. 90.5 and 91 vs. 94), did not reach a statistically significant level (Amin et al. 2006b; Krushell and Fingeroth 2007). Similarly, the improvement in KSS function scores (difference between the pre-operative and post-operative scores) were significantly lower for morbidly obese, however, improvement in KSS knee scores though lower in morbidly obese, failed to reach a statistical significance. Subgroup analysis between morbidly obese patients (BMI $\geq$ 40 kg/m^2) with the non-obese group (BMI < 30 kg/m^2) revealed

both pre-operative and postoperative KSS scores in the morbidly obese group as significantly lower at five years in the study by Foran et al. (2004)b.

For WOMAC scores however, no differences were seen in the baseline scores or 12 month follow up scores between severely obese (BMI $\geq$ 35 kg/m^2), and controls (BMI $\leq$ 35 kg/m^2) by Nunez et al. (2010). Rajgopal et al. (2008) reported worse WOMAC score at both baseline and 12 month follow up,but they reported no difference in the improvement of score (from baseline to follow up) between morbidly obese and the controls (BMI < 40 kg/m^2).

For the overall health related quality of life measured by SF12, as mentioned above, Dowsey et al. (2010) saw a significantly lower one year post-operative SF12 physical component score in the morbidly obese but no differences in the mental component score between morbidly obese, obese and non-obese. In contrast to this finding Rajgopalet al. (2008) reported a lower pre-operative and one year post-operative SF12 scores, the improvement in SF12 mental component score of morbidly obese group was significantly higher than the non-morbidly obese

4.4.7. BMI and clinical outcomes scores: Summary

From the review of the above literature for effects of BMI on questionnaire based functional outcomes, it is clear that differences exist in the results of the studies making it difficult to draw from it conclusively an effect of obesity. These differences in the evidence seem to be based around the following predominant factors:

1. Duration of follow up

   At short term follow up (up to one year), the results are conflicting, with Dowsey et al. (2010) reporting lower KSS scores for obese and morbidly obese while Deshmukh et al. (2002); Stickles et al. (2001); Nunez et al. (2010) reporting a lack of association of BMI with adverse outcomes assessed using KSS and WOMAC.

Evaluation of long term effect of obesity on KSS at follow up from 10 -15 years show a decreased score and therefore decreased function in the obese at follow up (Griffin et al. 1998; Foran et al. 2004a;). However for HSS score at long term, while a lower post-operative function was seen at 9.2 years for obese (Jackson et al. 2009), a lower pre-operative HSS for obese but similar follow up HSS scores between groups were also reported (Griffin et al. 1998).

In a second study by Foran et al. (2004b), a poorer absolute follow up KSS score as well as less improvement in the scores (from baseline to follow up at five year) for the obese patients was reported. However, other studies with similar or slightly longer follow up (two years to seven years) have been unable to demonstrate a poorer outcome in obese compared to non-obese (Spicer et al. 2001; Amin et al. 2006; Bourne et al. 2007; Dewan et al. 2009).

Therefore, conflicting results were observed for all different durations of follow up (one year to nine years). At a greater follow up, after ten to 15 years of surgery, poorer KSS scores in obese (BMI >30 kg/m^2), particularly in the function component has been reported though by only two studies with different study designs (Griffin et al. 1998; Foran et al. 2004a;). These disparities' in the results therefore make it difficult to conclude if there is a true effect of BMI on outcomes scores and if there is, the time point beyond which higher BMI patients are pre disposed to poorer function.

2. Questionnaire used

The questionnaire used most commonly in the studies in this population is the KSS and the WOMAC questionnaire has been predominantly used among the self-report questionnaires. Differences were seen between the two components (knee and function) of the KSS score. Some studies have reported low function component of KSS scores in obese (Griffin et al. 1998; Spicer et al. 2001; Jackson et al. 2009). Function component of KSS and HSS include assessment of walking and stair case climbing ability. In the study by Griffin et al. (1998), the average score for walking ability in obese was comparable to non-obese but the stair climbing ability was significantly lower in obese which lowered the overall KSS function score. In a

separate analysis of stair case climbing ability using self-report questions (Stickles et al. 2001), it was found that as BMI increased the difficulty in ascending and descending stairs increased at a one year follow up. Authors (Griffin et al. 1998) propose that since the patello femoral joint reaction forces reaches up to seven to eight times body weight, in an obese patient, this is more likely to cause pain after surgery. Jackson et al. (2009) also suggest that the decreased range of motion due to apposition of soft tissues at higher flexion angle would likely affect function in the obese.

For self-reported knee outcomes such as the WOMAC the literature seems to be consistent in concluding similar outcomes for obese and non-obese (Stickles et al. 2001; Nunez et al. 2010). Patient reported satisfaction with surgery was also equal among obese and non-obese patients. This could suggest that even though function when assessed objectively by examiners for knee replacement patients based on clinical parameters may be poorer for obese patients, the patients perception of the improvement in their function and satisfaction with surgery is comparable between obese and non-obese (BMI < or $\geq$ 30 kg/m^2).

The greater difficulty in function particularly stair ascending and descending in the obese patients (BMI $\geq$30 kg/m^2) has been evidenced by some studies lending support to the hypothesis that increased body mass adds to difficulty in performing joint loading activities. However this is refuted by evidence from other authors. Multiple factors such as cardio-vascular status, respiratory difficulties, pain or disability in other joints which affect activity performance contribute to functional difficulty. Though it can be supposed that comorbidity would be greater in obese which could contribute to the differences in the results.

3. Patients with BMI $\geq$ 40 kg/m^2 (morbidly obese)

Results of studies are more consistent when comparing KSS scores for morbidly obese and non-obese with the conclusion that the morbidly obese with BMI $\geq$ 40 kg/m^2 have a significantly lower function than the non-morbidly obese with BMI < 30 kg/m^2 (Foran et al. 2004b; Amin et al. 2006b; Krushell and Fingeroth 2007). On

comparison of BMI ≥ 40 kg/m^2 with BMI < 40 kg/m^2Winiarsky et al.(1998) also reported poorer KSS scores in the morbidly obese group. Self-report knee function measured by improvement in the WOMAC scores from baseline to follow up of one year in morbidly obese was comparable to non-obese (Rajgopal et al. 2008; Nunez et al. 2010). This again suggests that even at higher BMI, though the objective measure of function may not be comparable in the morbidly obese patients, patient's perception of function and health seems to improve comparably across BMI groups.

4. Influence of baseline scores

Clinical outcome has been analyzed as absolute follow up scores and as improvement of scores. When assessing absolute scores, the following striking differences were seen:

a. Comparable baseline scores between obese and non-obese but lower follow up scores in obese (Foran et al. 2004a; Foran et al. 2004b; Jackson et al. 2009, Dowsey et al. 2010).
b. Comparable scores between obese and non-obese at baseline and follow up (Amin et al. 2006a; Dewan et al. 2009; Nunez et al. 2010)
c. Lower baseline score in obese but comparable follow up scores between obese and non-obese (Spicer et al. 2001, Griffin et al. 1998 for HSS score).
d. Lower function component in obese at follow up, however, no baseline KSS data collected (Griffin et al. 1998 for KSS score).

The above differences raise questions regarding the influence of the baseline scores in studies and reflect the study design used to assess clinical outcomes scores. In order to minimize the above said influence, some studies have used controls matched for baseline scores (Foran et al. 2004b; Krushell and Fingeroth 2007; Nunez et al. 2010) or assessed improvement in scores from baseline to follow up in addition to or instead of absolute scores (Stickles et al. 2001; Nunez et al. 2010; Dowsey et al. 2010; Jackson et al. 2009; Bourne et al. 2007). Nevertheless, differences in results still persist rendering the true effect of obesity unclear.

Table 3 Details of previous studies assessing BMI and KSS scores

Study	BMI cut off	N (Obese vs Non-obese)	Follow up	Absolute scores		Change KSS scores
				Pre op KSS	Post op KSS	
Foran et al.(2004b)	30	68 vs. 68(matched)	6.6 years	Not different*	Lower in obese KSS knee (p =0.04), ES = - 0.39 KSS function (p=0.05). ES = - 0.3	Lower in obese KSS knee,p= .01, ES = 0.43
Griffin et al. (1998)	30	22 vs. 34	10 years	No baseline KSS	Lower in obese KSS function (63.7 vs. 82.2), p< 0.01	
Foran et al. 2004a	30	27 vs. 27 (matched)	15 years	Not different*	Lower in obese KSS knee (81 vs. 89), p = .019	
Amin et al. 2006a	30	125 vs 158	5 years	Not different*	Not different* 84.1 vs. 85.8	
Spicer et al. 2001	30 (5 groups)	285 vs. 371	6.3 years	Lower in obese KSS function, p = <0.01 for BMI = 35-39.9 and BMI >40	Not different* 77.2, 77.9, 72.9 (obese groups) vs. 79.5 (non-obese group)	Not different* 41.1, 44.9, 40.1 (obese groups) vs. 40.2 (non-obese

Dewan et al. 2009	3 groups (30-39) (≥40) vs <30	71,31vs 67	5.4 years	Not different*	Not different* KSS knee = 88, 85 (obese) vs. 83 (non-obese) KSS function = 71,68 (obese) vs. 66	
Dowsey et al. 2010	30 (3 groups) 30-39, ≥40 Vs. <30	261, 57 vs. 211	1 year	Not different*	Lower in obese and morbidly obese KSS kee and function, p <0.01	Lower in obese and morbidly obese KSS function, p = 0.006 Total KSS, p = 0.016
Winiarsky et al. 1998	40	40 vs. 1539	5 years	Not different*	Lower in morbidly obese KSS knee (84 vs.92) and KSS function (53 vs. 67), p<0.001	
Amin et al. (2006b)	40 (≥ 40 vs. < 30)	38 vs 38 (matched)	3.2 years	Not different*	Lower in morbidly obese KSS function, 75.6 vs. 83.4, p= 0.01	
Krushell et al. 2007	40 ≥40 vs. <30	39 TKA vs 39 matched TKA	7.5 years	Not different*	Lower in morbidly obese KSS function (44 vs. 64), p<0.01	Lower improvement in morbidly obese KSS function (16 vs. 26)
Deshmukh et al. (2002)	BMI as continuous variable		1 year		BMI accounts for insignificant amount of variation (13%) in scores	

*No statistical significant difference

Table 4 Details of previous studies assessing BMI and HSS scores

Study	**BMI cut off value (kg/m^2)**	**N (obese vs. non-obese)**	**Follow up**	**Absolute scores**		**Change/Improvement in HSS scores**
				Pre op HSS	**Post op HSS**	
Griffin et al. (1998) BMI <30 vs BMI>30	30	22 vs. 34	10 years	Lower in obese 47.7 vs 55, $p < 0.01$	Not different* (88.3 vs 90.3)	
Jackson et al. (2009) BMI <30 vs BMI>30	30	50 vs. 50 (matched)	9.2 years	Not different*	Lower in obese (83.8 vs. 87.4), $p < 0.05$, ES = -0.4	Less improvement in obese (27.3 vs. 33.3), $p < 0.05$ ES = -0.39

*No statistical significant difference

Table 5 Details of previous studies assessing BMI and WOMAC scores

Study	**BMI cut off value (kg/m^2)**	**N (obese vs. non-obese)**	**Follow up**	**Absolute scores**		**Change/Improvement in WOMAC (total) scores**
				Pre op WOMAC	**Post op WOMAC (total)**	
Sticles et al. 2001	<25 25-29 30-34 35-39 ≥40	271, 149, 92 vs. 146, 204	1 year	Poorer scores as BMI increased, $p < 0.01$	Poorer scores as BMI increased, $p < 0.01$	Not different* 23.1, 25.3, 26.7 vs. 20.6, 23.4
Nunez et al. 2010	35	60 vs. 60 (matched)	1 year	WOMAC stiffness lower (better) in non-obese 53.3 vs. 37.9	Not different* 28.3 vs. 28.6, ES = -0.016	Not different* 33.1 vs. 29.6 (ES of change form baseline for each group = 2 vs. 2.2)
Rajgopal et al. 2008	40	69 vs. 481	1 year			Not different* $p = 0.669$ (mean values not given)

*No statistical significant difference

Table 6 Details of previous studies assessing BMI and SF36 or SF12 scores

Study	BMI cut off value (kg/m^2)	N (obese vs. non-obese)	Follow up	Absolute scores		Change/Improvement in SF36/SF12 scores
				Pre op SF36/SF12	Post op SF36/SF12	
Sticles et al. 2001	<25 25-29 30-34 35-39 ≥40	271, 149, 92 vs. 146, 204	1 year	Lower scores as BMI increased (PCS and MCS), p < 0.01	PCS = 38.3, 37.3, 37.9 vs. 40.2, 40, p <0.05 MCS = 53.7, 52, 52.5 vs. 53.6, 54.8, p< 0.05	Not different* PCS = 8.3, 9.5, 9.9 vs. 8, 9.3 MCS = 0.7, 0.8,1.2 vs. 1, 0.5
Steven-Lapsley et al.2009	BMI as continuous variable	106	1 month,3 months and 6 months			BMI did not account for variation in SF36 r = 0.39 (1 month), 0.49 (3 months), 0.47 (6 months)
Dowsey et al. 2010	30 30-39, ≥40 vs. <30	261, 57 vs. 211	1 year	Not different*	Lower in morbidly obese PCS (SF12) = 31.1 (morbidly obese) vs. 36.3 (obese), 35.8 (non-obese), p = 0.05	Not different* PCS = 9.9 (obese), 5.3 (morbidly obese) vs. 9.4 MCS = 0.4 (obese), 3.3 (morbidly obese) vs. 0.7
Rajgopal et al. 2008	40	69 vs. 481	1 year	Lower in morbidly obese PCS (SF12) = 31.8 vs. 34.8 MCS = 49.6 vs. 54.3	Lower in morbidly obese p<0.05 (mean values not given)	Improvement in MCS more in morbidly obese p < 0.05

4.5. Radiological evaluation and prosthesis longevity

A significantly higher incidence of focal osteolysis was seen in obese patients; 13 in obese (n = 285) vs. 5 in non-obese (n = 371) (Spicer et al. 2001). However, in this study with an average follow up of six years though revision rates in obese exceeded that in non-obese (16 in obese vs 13 in non-obese), using revision of any component as end point for survival, survivorship analysis showed statistically similar survival rates between obese and non-obese (98.1% for obese and 99.9% for non-obese). This similarity was maintained till the tenth year which was the last follow up. Amin et al. (2006a) on the other hand saw comparable revision rates between obese (four revisions) and non-obese (three revisions). Slight asymmetry of polyethylene space (less than 1 mm) between medial and lateral compartments was seen in six patients (four obese, two non-obese) by Griffin et al. (1998) in their sample of 56 patients. There were significantly more non progressive radiolucent lines in the obese group compared to the non-obese. However, this did not have any implications on prosthesis survivorship in this study as all three knee replacements revised were in patients in the non-obese group.

Some studies classified the result of TKA as ‘failure’ or ‘success’ based on need for revision or a combination of need for revision and clinical outcome scores.

Vasques-vela Johnson et al. (2003) investigated the effect of patient demographics (BMI, age gender, diagnosis) in 559 TKA. They considered ‘failure’ as revision operation or prosthetic component removal. Prosthesis survival rate according to this study was 92.7% in obese compared to 98.5 % in non-obese showing good results were obtainable in obese patients but they are not as good as the ten year survival rate in the non-obese. In this study survival rates were seen to be lowest at 35.71% in obese patients with age less than 60 years. Bordini et al. (2009) considered revision of at least one component or exchange of polyliner as the end point for prosthesis survival, in a retrospective review of a large database with 6532 non-obese patients and 3203 obese patients. They did not find any influence of BMI on the survival of prosthetic implant at five years follow up with similar failure rates across BMI groups. In contrast to these findings, On the other hand, Mulhall

et al. (2007) assessed the patient reported time between primary TKA and revision surgery in 291 patients undergoing revision TKA and found that the average survivorship time was significantly lower in obese compared to non-obese (6.6 years in obese vs. 8.3 years in non-obese). Failure of TKA as described by a fair/poor post-operative KSS score or revision surgery or radiographic failure was of a significantly higher rate in obese compared to non-obese in the study by Foran et al. (2004b). Eighty eight percent of knees were considered to have a successful outcome in the obese group with four patients undergoing revision surgery while 99% of the non-obese patients had a successful outcome with no revisions in the group (at an average follow up of 6.6 years). Survivorship curves to analyze the differences in time to prosthetic failure showed similar rates of prosthetic survival between the obese and non-obese, until between 5 and 6.6 years after which failure rate became more apparent in obese patients. In a similar study by Foran et al. (2004a) with a longer follow up duration of 15 years, the failure rate in obese patients at the last follow up at 15 years post TKA was higher than non-obese patients but not statistically significant (9 vs 3 of 30 knees). Survival analysis revealed similar rate of prosthetic failure between obese and non-obese however, lower survival rates became apparent in obese patients by 15 years. Rate of polyethylene spacer change was also greater in non-obese than obese (though not statistically significant). However, it was noted that the overall activity level of patients undergoing polyethylene spacer change was higher compared to those not undergoing a polyethylene spacer change.

4.5.1. Prosthesis survival in morbidly obese patients (BMI ≥ 40 kg/m^2)

Amin et al. (2006b) compared the results of TKA between 38 morbidly obese patients and 38 non-obese controls matched with a mean follow up of 3.2 years. In the morbidly obese group, apart from lower KSS scores and significantly higher rate of overall complications (superficial wound infection, deep joint infection, deep vein thrombosis, peri-operative mortality), higher rate of radiolucent lines around the implants were seen. Five year survivorship using revision as end point was 74.2% in morbidly obese and 100% in non-obese (BMI < 30 kg/m^2) and when using revision and pain as end points, was 72.3% in morbidly obese and 97.6% in non-obese. Both five year survivorship rates

were statistically different between the two groups. At an average follow up of 7.5 years, though higher revision rates were seen in morbidly obese compared to the control groups with BMI < 30 kg/m^2 (2 vs. 0), the difference, however, did not reach a statistically significant level (Krushell and Fingeroth 2007). Differences in revision rates between morbidly obese (BMI $\geq$ 40 kg/m^2), obese (BMI = 30-39 kg/m^2) and overweight (BMI = 20-29 kg/m^2) also did not reach statistical significance at 5.4 years (Dewan et al. 2009). With regard to radiolucencies, three studies (Winiarsky et al. 1998, Mont et al. 1996 and Krushell and Fingeroth 2007) did not report significant differences between morbidly obese (BMI $\geq$ 40 kg/m^2) and non-obese (BMI < 30 kg/m^2) or non-morbidy obese (BMI < 40 kg/m^2) at follow ups of five, seven and 7.5 years respectively.

4.5.2. BMI and prosthesis survival: Summary

A summary of the findings of the key studies are shown in Table 7.

Prosthesis survival is one of the important measures of long term results of total knee replacement. The effects of obesity on implant survival assessed by the above studies use different end points to describe survival. While some studies use survivorship analyses, many studies use revision rates and/or radiographic analysis and/or poor clinical scores to determine the success and failure of the procedure. Many studies showed a lower survival rate in obese patients (BMI $\geq$ 30 kg/m^2) in comparison to that in non-obese patients (Vasquez Vela Johnson et al. 2003; Foran et al. 2004a; Foran et al. 2004b; Mulhall et al. 2007). On the other hand, some studies found equal survivorship in obese and non-obese (Griffin et al. 1998; Amin et al. 2006a; Bordini et al. 2009; Jackson et al. 2009). Evidence from the studies reporting decreased survivorship in obese patients has supported the hypothesis that increased body mass and therefore increased mechanical loading on the prosthesis during weight bearing activities can lead to increased wear and tear with time. This is further supported by the evidence of the lowest 10 year survival rate in the younger obese patients (BMI $\geq$ 30 kg/m^{2}and age < 60 years) in one study (Vasquez Vela Johnson et al. 2003). The assumption of greater activity levels in younger patients highlights the compounded effect of increase loading with addition body mass and

repeated loading activities on the durability of prosthesis. Revision due to prosthetic infection could be suggestive of a higher rate of prosthetic infection at mid - term (5 years) or long term. Based on this hypothesis of increased loading, more obvious and consistent evidence of decreased prosthetic survival can be expected from studies comparing morbidly obese and non-obese/non morbidly obese. However, as inferred from the section above, this is not the case and that differences in results still persist even with the morbidly obese group. Similar prosthetic survival or revision rates between obese/morbidly obese and the non-obese patients gives support to an alternate hypothesis by authors that because wear and tear of prosthesis is a function of use, lower activity levels in higher BMI patients would compensate for the additional load on the joint.

Table 7 Radiograhic Evaluation and Prosthesis survival

Study	**Sample (obese vs. non-obese) and Duration**	**Independent Variable(s)**	**Results**
Foran et al. 2004	27 vs 27 control 15 years	BMI≥30 BMI<30	Polyethylene spacer revision in 33% obese compared to 60% non-obese,p = 0.069 Success rate (KSS>79, revision due to aseptic loosening, radiographic signs of failure) = 70% in obese vs. 90% in non-obese, p 0.102
Griffin et al. 1998	22 vs 34 10.5 years	BMI≥30 BMI<30	3 (9%) revisions in non-obese vs. 0 in obese
Vasques-vela Johnson et al. 2003	138 vs. 301 10 years	Age Gender BMI	Overall survival rate at 10 years in obese 92.7% vs 98.5% in non-obese, p < 0.01 66% of failed knee in obese group
Spicer et al. 2001	285: vs 371: 10 years	BMI>30: <30: control	Rev rate higher in obese (5.6% vs. 3.5%), p = 0.25, Radiographic osteolysis in obese = 13 vs 5 in non-obese, p <0.05

Foran et al. 2004	68 vs. 68 (matches) 5-7 years	BMI>30: <30:	4revisions in obese = 4 vs 0 in non-obese After 6.6 years, prostheric survival rate of 87,7% vs. 98.7% in non-obese (re operation, clinical failure, radiographic failure as end points)
Bordini et al. 2009	8892 18 months – 5 years	BMI<25 25-30 30-35 >40	Failure/revision due to any reason was similar across groups 1.9%, 2.3% (>30) vs. 2% 1.9% (< 30)
Mulhall et al. 2007	291 undergoing revision surgery	BMI	Avg survivorship time for primary prosthesis significantly lower in obese (77.2 vs 99 months), p = 0.036
Amin et al. 2006a	125 vs 158 5 years	BMI: BMI>30: <30:control	2.5% revision in obese vs. 1.4%, not statistically significant
Amin et al. 2006b	38 vs 38 5 years	BMI>40: <30 control	Overall results for morbid obese inferior compared to non-obese
Krushell and Fingeroth (2007)	39 vs 39 5 – 14years	BMI>40: <40 control	Most M.ob have long term improvement in pain, function but less frequently than non-obese

4.6. Other influences

Apart from the various differences in the literature assessing obesity and outcomes after TKA such as study design, outcome measure and obesity classification, there are other influences on the outcomes of the surgery, which may overlap with the effect of obesity or independently affect the patient resulting in a good or poor outcome. In the section below, the influence of weight change after surgery, activity levels, previous and subsequent contralateral TKA and personal factors will be discussed to understand the relation between these factors and obesity and their effect on the overall outcome of TKA.

4.6.1. Physical activity

Prosthetic wear is a function of use i.e., greater the use (measured as physical activity) of the implant knee, faster is the rate of wear (McClung et al. 2000). Laboratory studies have shown that greater wear is proportional to the load. Therefore it is suggested that in obese TKA patients since there is a greater load due to the higher body mass, wear could be greater with use when compared to non-obese (Gillespie &Porteous 2007). However no consistent relationship between body mass of patient and polyethylene wear has been seen in the literature. In general, obesity is associated with lower physical activity i.e., lower energy expenditure during leisure time (Gonzalez et al. 1999). Specific to the TKA population, only a few studies have investigated the association of obesity and activity and relation to outcomes. McClung et al. (2000) saw a significant negative association of obesity ($p = 0.008$, $r^2 = 0.79$) with physical activity as measured by pedometer, after adjusting for age, gender and Charnley class in knee arthroplasty patients. Schmalzried et al. (1998) on the other hand did not correct for age and gender and did not see any significant association of body weight with the number of steps taken in their total sample of knee and hip arthroplasty patients ($p = 0.75$). However on separating gender, they noticed a stronger association of decreased walking activity with increasing weight (adjusted for height) in women though not statistically significant ($p = 0.09$, 'r' values for

this study were not given). McClung et al. (2000) also saw lower activity levels and higher body mass in their TKA patients compared to THA patients thus suggesting some association of obesity and physical activity levels after a total knee replacement. One of the suggestions of the studies showing no effect of BMI on TKA outcomes is that the lower activity levels in obese patients compensates for the functional difficulty due to increased loads. However, with no association seen between weight and physical activity after arthroplasty by Schmalzried et al. (1998) and no difference in the activity levels between obese and non-obese TKA patients in the study by Foran et al. (2004a), lower activity level in obese TKA patients cannot be concluded. Participation in physical activity is influenced by a number of other factors which may have a stronger association than obesity such as pain, age (Sequeira et al. 1995; Schmalzried et al. 1998) and gender related differences related barriers to participation (Ball et al. 2000). In addition, generalized arthropathy and patient's impression of their perceived performance ability may also affect their actual performance. Moreover in short term, it had been seen that activity participation improves from three months after surgery (Davis et al. 2011) probably due to initial phases anxiety and kinesiophobia related to wound healing and damaging the replaced knee.

Naal and Impellizzeri (2010) in their systematic review of physical activity in TKA patients conclude that the physical activity levels are less than the recommended activity levels for health enhancement. But when compared to controls with osteoarthritis (being treated medically), TKA patient have been reported to have a higher activity level and better cardiovascular health (Reis et al. 1996). The main purpose of TKA is pain relief and restoration of joint function and because it is an elective procedure, the patient's perception of success of the surgery will depend upon the individual goals of post-operative function and activity. Reflecting this assumption, Weiss et al. (2002) found that TKA patients participate in a wide range of therapeutic and recreational activities and their participation ability depends on specific activity which may impose different loads and motions on the knee than that judged by walking. Thus, the physical activity levels in TKA patients after surgery is varied and is dependent on various factors including patients preference of the type of activity, however, despite the link between obesity and lower activity in the general population, if physical activity levels after TKA are

particularly less in obese is unclear and is confounded by a number of other patient characteristics.

4.6.2. Weight change after TKA

Some surgeons recommend weight loss prior to TKA when obesity is seen as a risk for complications and difficulty in procedure. While exercise participation is one of the primary methods recommended for weight loss, pain and symptoms of arthritis are most commonly cited by patients as barriers to exercise participation and that relief of symptoms is a potential motivating factor for exercise participation (Wilcox et al. 2006). Hence there is an expectation that symptom relief after TKA would enable exercise participation and subsequently weight loss. However studies assessing weight change after TKA do not support this conclusion. With follow up ranging from one to two years, studies did not find a significant loss in weight after TKA (Woodruff and Stone 2001; Heizel et al. 2005; Donovanet al. 2006; Lachiewics and Lachiewics 2008; Dowsey et al. 2010; Zeni and Snyder-Mackler. 2010). In fact, some studies saw a higher proportion of patients gaining weight after surgery. Twenty one percent gained > 5% pre-operative weight versus 14% who lost >5% pre-operative weight in the study by Dowsey et al. (2010)and this proportion were 23% (gained) versus 17% (lost weight) in the study by Lachiewics and Lachiewics (2008) and 66% (gained) versus 34% (lost) was seen by Zeni et al. (2010). Increase in weight especially in the obese would be a cause for concern as it would put them at a higher health risk and greater asymmetrical loading on the knee joints. Pre-operative BMI was not seen to influence weight change after TKA (Dowsey et al. 2010; Zeni et al. 2010). Pre-operative function level also did not have an effect on weight change (Dowsey et al. 2010; Zeniet al. 2010) but age was found to be significantly associated with weight loss $\geq$ 5% pre-operative weight (Dowsey et al. 2010) Thus from the literature it seems that mobility achieved after TKA does not result in weight loss and greater BMI does not mean a greater weight gain or loss after TKA. Since loss of weight appears to be independent of functional recovery and activity after TKA therefore; expectations of some patients regarding weight loss as a result of surgery may not be realistic.

4.6.3. Contralateral knee disease and other joint disease

Hawker et al. (1998) in their survey saw a poorer WOMAC score in those with contralateral knee disease. Poorer performance in 15 minute walk test, slower recovery in the stiffness and function domain of WOMAC and physical function domain of SF36 after knee or hip arthroplasty was seen in patients with severe other joint disease (Naylor et al. 2008). However, the pain and global improvement was significant irrespective of the presence of other joint disease. The ten year risk of a contralateral knee replacement is also observed to be as high as 37-63% (McMohan and Block 2003). Thus, clearly the presence of other joint disease will affect the recovery and outcomes after TKA. Patients with other joint disease would also tend to have lower pre-operative functional status, however, the study by Naylor et al. (2008) did not see significant differences in baseline WOMAC scores between those with and without other joint disease.

Functional performance after TKA is strongly related to muscle strength in both operated and non-operated limb but more strongly to that in the non-operated side (Mizner and Snyder-Mackler 2005). It was reported that during sit to stand activities, patients tend to shift weight away from the operated side to the non-operated and the asymmetry in quadriceps strength also show that the non-involved limb is used more for loading during post-operative recovery (Mizner and Snyder-Mackler 2005).

Therefore, the presence of disease in the non-operated knee and other lower limb joints may cause increased difficulty during weight bearing activities, compromised recovery of function in the operated side, thus also reflected in the self-report outcomes (Hawker et al. 1998; Naylor et al. 2008). Moreover, when interpreting self-report score even though joint specific, patients may be unable to isolate the effect on the particular joint from the debilitating effect of the disease in other joints.

4.6.4. Personal factors

Mental health in TKA patients was not seen to be affected by BMI when measured as mental health component summary of SF36/SF12 pre-operatively or post-operatively (Stickels et al. 2001; Rajgopal et al. 2008; Nunez et al. 2010). However, pre-operative mental health scores have shown to have an effect on the outcomes in other studies (Heck et al. 1998; Fisher et al. 2007).

Patient expectations of improvement and optimism have been shown to have certain degree of influence on pain and functional outcomes in arthroscopy patients (Moseley et al. 2002). Patient's expectations and optimism would be reflected in their level of motivation and active participation in the post-operative rehabilitation which is considered important for recovery (Fisher et al. 2007) and in turn various psychological determinants both affective and cognitive will affect the patient's expectations from the procedure and expectations of their own self efficacy. Pain coping, recovery locus of control i.e., recovery is self-dependent or on others (doctors, healthcare workers, fate), and level of pain coping or pain catastrophizing is associated with avoidance of pain inducing activity which can affect the achievement of functional goals after TKA (Kendall et al. 2001). Jones et al. (2007) in their review acknowledge that while the evidence on the effect of psychological variables on pain and function is sparse, early evidence in fact suggests that psychological determinants have a greater influence than medical or baseline variables on pain and function after TKA.

4.7. Conclusion

Increased risks of post-operative complications and deteriorating effects of obesity on post-operative health have been well documented for obese patients. However, this could not be clearly concluded for TKA patients from the literature because of discrepancy in the reported evidence. The comparison of results of the studies was difficult due to the

differences in the methodological approach, differences in the stratification of the levels of obesity and also the different approaches applied in the literature to define and classify outcomes.

Overall, the results of the studies show that the effect of obesity as measured by BMI is unclear and it is difficult to indicate a specific cut off point, the BMI beyond which is a definite risk of poor post-operative health. However, a negative effect of BMI on outcomes has been detected more consistently when morbidly obese (BMI $\geq$ 40 kg/m^2) are compared with non-obese (BMI < 30 kg/m^2). Though an association of increased post-operative health risk after a surgical procedure with increasing BMI has been established, it not as striking as one would expect in the TKA population. TKA is an elective orthopaedic procedure and patients with considerable existing comorbidity and therefore possessing significant health risks post-operatively are typically screened for evaluation and treatment before proceeding to surgery which could work to decrease the complication rates in all patients.

At 10-15 years after TKA, evidence has been reported for poorer function in patients with BMI $\geq$ 30 kg/m^2. This would suggest an adverse effect of obesity developing in the longer term. However, the time point after which obese patients are predisposed to these adverse outcomes is inconclusive as only two studies in the review have evaluated the effect of BMI on outcomes (KSS) at long term follow up (Griffin et al. 1998, 10 years; Foran et al. 2004, 15 years after surgery). The evidence is further limited by the differences in study design (matched control vs. non matched design), lack of baseline KSS data in one study (Griffin et al. 1998) and small sample size (27 obese and non-obese vs. 22 obese and 34 non-obese). Evidence for the effect of BMI at midterm (5-9 years follow up) and short term (one year follow up), remain inconsistent and therefore difficult to conclude.

Poorer knee function scores have been observed in studies finding a negative effect of BMI on outcomes (Griffin et al. 1998; Foran et al. 2000b; Jackson et al. 2009; Dowsey et al. 2010). The lower function scores in obese compared to non-obese according to some authors is due to lower ability in stair ascending and descending and patello-femoral pain during certain activities (Griffin et al.1998; Stickles et al. 2001). Patello-femoral joint

reaction forces during activities like stair climbing is about 3.3 times body weight and reach up to 8 times the forces produced during walking (Reilly &Marten 1972, Costigan et al. 2002) . The resultant forces produced could reach pain threshold for some obese during stair ascending and descending who otherwise have comparable walking ability. In addition, poor cardio-vascular status, respiratory disease and other joint disease/disability which assumed to be more likely in obese could also influence performance in these activities.

Little or no adverse impact of obesity on self-report knee function (WOMAC) or self-reported general quality of life (SF36, SF12) has been reported more consistently in the literature. Similarly, satisfaction with surgery has been seen to be comparable between obese and non-obese. These suggests that while objective measures based on clinical parameters, measured by an examiner may or may not be poorer in obese and morbidly obese patients, the perception of function at knee and quality of life and satisfaction with a knee replacement surgery is significant in all patients irrespective of their BMI.

It is hypothesized that with increasing body mass, greater load is put on the prosthesis which over a period of time causes wear and tear of the prosthesis or prosthetic loosening. Several studies in the review show a lower prosthesis survival rate in obese when compared to non-obese patients (Winiarsky et al. 1998; Vasquez Vela Johnson et al. 2003; Foran et al. 2004a; Amin et al. 2006; Mulhall et al. 2007). However, some studies show equal implant survivorship (even at 10 years follow up) between the obese and non-obese groups (Griffin et al. 1998; Amin et al. 2006; Bordini et al. 2009). This was reasoned by the lower activity level in obese as wear and tear of the prosthesis had a direct association with activity levels. Obese patients with added stress on the prosthesis but with lower activity levels might have the same degree of prosthetic wear and tear as a non-obese patients assumed to have higher activity levels. Also, the additional weight in obese may be less than the level of stress which would predispose an early failure. This again highlights the lack of uniformity due to differences in the cut off value of BMI used for stratification of obese and non-obese.

In studies specifically assessing patients with BMI $\geq$ 40 kg/m^2, consistency in evidence may be suggestive of poorer outcomes compared to non-obese. However, the sample

numbers for morbidly obese are less in many studies for the results to reach a statistical significance. At long term, outcomes for patients with BMI greater than 30 kg/m^2 seem to be less favorable. However, there is very limited evidence for this. With the increasing numbers of TKA performed, prevalence of obese patients in the TKA population and the consequent implication of increasing health costs, it is important to establish if obese patients have results comparable with non-obese TKA or have to live with compromised results after TKA.

4.7. Chapter summary

This chapter described the findings of the literature review undertake to evaluate the effect of BMI on outcomes after TKA. Findings of the effect of BMI on post-operative complications, functional outcomes and prosthetic longevity was discussed which revealed the inconsistencies in the evidence due to differences in methodological approach and classification of BMI and outcomes. The present evidence from literature shows that it is difficult to confirm an effect of BMI which would result in failed or compromised results. While differences were largely seen in studies using a BMI cut off value of 30 kg/m^2, more consistent evidence was seen for a negative effect of higher BMI values (BMI $\geq$ 40 kg/m^2) on outcomes.

Considering the disparities existing in the reviewed studies, the following chapters in this thesis aim to evaluate the effect of obesity on TKA outcomes in the following two studies:

1. A retrospective review of the effect of BMI on the self-report outcomes at up to one year following TKA.
2. A prospective evaluation of the effect of obesity as measured by five body composition methods on the self-report outcomes at up to one year following TKA.

CHAPTER 5: RETROSPECTIVE REVIEW OF THE EFFECT OF BMI ON TKA OUTCOMES

5.1. Chapter overview

This chapter presents the retrospective evaluation of the effects of BMI on outcomes one year following TKA. The rationale and aims for the study are presented after which the protocol followed for the study has been detailed. The results of the study have then been reported followed by a discussion of the findings of the study. Finally, a summary of the chapter is presented.

5.2. Introduction

Obesity has been defined according to the Body Mass Index (BMI), where a BMI above 30 kg/m^2 is considered obese (World Health Organisation. 2000). It has been seen that BMI increases with age reaching a peak incidence in the age group of 60- 69 years coinciding with the average age range for primary joint replacement (Crowninshield et al. 2006). The global increase in the prevalence of obesity in the total knee arthroplasty population has led to concerns regarding the outcomes of the surgery in obese patients. Obesity is considered as a risk factor for a number of surgical complications and there also remain concerns about the impact of the added stress on the underlying bone and implant material in obese patients thereby affecting the prosthetic longevity and functional gain (Winiarsky et al. 1998; Miric et al. 2002; Mulhall et al. 2007.). The question whether obese total knee arthroplasty patients are predisposed to adverse outcomes, has been researched previously with conflicting results. On defining obesity as

BMI greater than 30kg/m^2, several studies reported no significant difference in the outcomes in obese and non-obese patients (Spicer et al. 2001; Stickles et al. 2001; Deshmukh et al. 2002; Amin et al. 2006a), while other studies show obese patients with inferior outcomes in terms of post-operative complications, function and revision rates (Griffin et al. 1998; Foran et al. 2004a; Foran et al. 2004b; Namba et al. 2005).

Most of the previous literature on obesity in TKR is centered on surgical aspects and surgeon/investigator measured outcomes. The Knee Society Score (KSS) has been most commonly used outcome measure in these studies (Griffin et al. 1998; Winiarsky et al. 1998; Spicer et al. 2001; Deshmukh et al. 2002; Foran et al. 2004a; Foran et al. 2004b; Amin et al. 2006a; Amin et al. 2006b; Krushell and Fingeroth 2007). Few studies assessing the impact of obesity on total knee replacement outcomes have focused on the use of patient administered outcomes. Patient's perception of their functional difficulties specific to their health problem and their perception of their general quality of life can provide a complete evaluation of their perceived benefits of the intervention. In the review of the literature in Chapter 4, it was found that comparison of the short term follow up (one year) of self-report questionnaires specific to knee function such as the WOMAC, between obese and non-obese patients was undertaken by a few number of studies with different BMI classification of obesity (Stickles et al. 2001using a five groups comparison, Nunez et al. 2010 using BMI <35 kg/m^2 vs. BMI $\geq$35kg/m^2 and Rajgopal et al. using BMI $\geq$40 kg/m^2vs. BMI < 40kg/m^2). No study has assessed self-reported knee function using the Oxford Knee Score (OKS) which is a questionnaire specific to TKA patients.

Furthermore, most previous studies have assessed patients from the databases or registers of different surgeons, adding to the heterogeneity of the sample and thus making it more difficult to find an effect of obesity.

Therefore, the purpose of this retrospective epidemiological evaluation is to assess the influence of Body Mass Index (BMI) on the patient perceived outcomes of TKR in patients undergoing total knee replacement under the care of a single surgeon The current study assesses patients' perception of their functional ability specific to their knee

replacement, as measured by Oxford Knee Score (Dawson et al. 1998) and also their quality of life as measured by Short Form 12 questionnaire (SF12) (Ware et al. 1996).

5.3. Aim of the study

The aim of the study is to retrospectively evaluate the effect of BMI on self-reported patient outcomes at six months and one year after surgery in patients who underwent primary TKA at the Royal Infirmary of Edinburgh between the years 2005 and 2008.

The null hypothesis for this study was that there is no effect of BMI on the self-reported patient outcomes at six months or one year after TKA.

5.4. Material and methods

5.4.1. Ethics

Ethical approval was sought and granted from the NHS Lothian Board Research Ethics Committee of the prior to the commencement of the study.

5.4.2. Participants

The number of participants was based on the availability of data of patients who had undergone primary total knee replacement surgery from January 2005 up to and December 2008 under the care of a single surgeon at the Royal Infirmary of Edinburgh. A total of 211 was case notes were available from the medical records library, of which

171 patients' data was included in the study (160 with osteoarthritis and 11 with rheumatoid arthritis). Forty cases were excluded from the evaluation for the reasons of diagnosis other than osteoarthritis/rheumatoid arthritis, missing pre-operative BMI data in case notes and relocation of files to other hospitals. Patient data included in the analyses satisfied the following inclusion criteria:

a. Primary TKA under the care of Mr. R Burnett (Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh) between January 2005 up to and December 2008.
b. Underlying diagnosis of osteoarthritis or rheumatoid arthritis of the knee.
c. Availability of patient's medical files with complete data regarding medical details, pre-operative BMI and post-operative care.

5.4.3. Surgery

All patients included in the study were operated using a similar surgical approach by a single surgeon with a medial parapatellar approach. Kinemax plus or Triathlon total knee replacements were used. Post-operative care and rehabilitation in the hospital is based on an integrated care pathway and was identical for all patients.

5.4.4. Data access and extraction

List of patients, who had undergone TKR under the care of the surgeon between January 2005 and December 2008, was obtained from the formic data collection system, Royal Infirmary of Edinburgh along with their gender, date of birth, SF12 scores, and OKS scores. The patient list was then given to the medical records library of the hospital with request for access of patient records.

The formic data collection system at the Royal Infirmary Edinburgh which was accessed to collect the questionnaire data (OKS and SF12) is a database that holds information on self-report questionnaires of patients who are admitted to the Royal Infirmary Edinburgh for elective orthopaedic surgery. For total knee replacement surgeries, the OKS and SF12

questionnaires are administered routinely to the patients prior to surgery; six months and one year after surgery as postal questionnaires. The scores obtained are stored in this database along with patient date of birth, gender, consultant and hospital number.

From the medical records accessed, BMI and demographic information (age, sex and initial diagnosis), date of surgery, date of discharge and previous medical history was extracted from the pre-operative assessment document. Any complications post-operatively were noted from the multidisciplinary clinical care pathway records and follow up case notes and grouped under local complications (wound leakage, wound hematoma, post-operative infection, local orthopedic complication) systemic complications (cardiac, respiratory, circulatory, neurological, gastro intestinal, genito-urinary complications and septicemia) and incidence of revision surgery (if patient has further undergone or been referred for a revision surgery).

5.4.5. BMI groups

BMI is defined as the body weight in kilograms divided by the square of the height in meters. Using the World Health Organization definition of obesity (WHO 2000), patients were divided into BMI groups of non-obese (BMI<30 kg/m²) and obese (BMI≥30 kg/m²).

5.4.6. Outcome measures

Pre-operative (one week prior to surgery), six months and one year follow up data was obtained for the Oxford Knee Score and Short Form 12 data.

Oxford Knee Score

Oxford Knee score (Dawson et al. 1998) is an assessment tool specific to the total knee replacement. It has been tested by its authors for internal consistency, test retest reliability, its construct validity with Knee Society Score, SF36 and Health Assessment

Questionnaire (HAQ) and sensitivity to change (Dawson et al. 1998). The authors describe the involvement of TKA patients in the derivation of the questionnaire's content in order to draw patient views on how their knee problems affect their lives to satisfactorily address patient concerns which they believe is essential for the instruments content validity. The questionnaire is considered sort and simple and has been shown to have a high completion rate compared to other self-report knee questionnaires including WOMAC and Lequesne Index of Severity- Knee (Dunbar et al. 2001).

The original scoring system for OKS consists of 12 equally weighted questions addressing patients' assessment of their knee function and its effects on their quality of life. Each question is scored from 1 to 5 with a minimum total score of 12 indicating least difficulty and a maximum score of 60 indicating most functional difficulties. The OKS data recorded in the hospital database were based on this system of scoring. This system of scoring has been criticized and unintuitive and several modifications to scoring by users have led to confusion (Murray et al. 2007). The developers of OKS recommend the use of a standard form of new scoring system where each question is scored from 0 to 48, with a minimum total score of 0 indicating most functional difficulty and a maximum score of 48 indicating least functional difficulty. Once scores were obtained from the database, they were converted into the new scoring system by subtracting each score from 60 as recommended by the authors.

No specific categories of the score are given to indicate levels from best to worst outcomes. However, it has been noted that like all outcome scores, the absolute score tends to decrease with age (Whitehouse et al. 2005). After a joint replacement, it is suggested that most improvement in function and in the OKS occurs within the first year after a TKA (Whitehouse et al. 2005).

It has been shown that the pre-operative scores for the questionnaire is one of the biggest determinants of the post-operative score (Whitehouse et al. 2005). Therefore, the authors (Murray et al. 2007) suggest that change in score should also be analyzed in addition to post-operative scores.

Short Form 12 questionnaire

The Medical Outcomes Study Short Form 12 Health Survey questionnaire (Ware et al. 1996)is an instrument used to measure overall physical and mental health. It also consists of 12 questions. It was adapted from the Medical Outcomes Study Short Form 36 Health Survey (SF36) by the developers of SF 36 (Ware et al. 1996) and shows close and linear association with SF36. The purpose of development of the SF12 was to reduce the number of health dimensions measured by selecting 12 items from the original 36 items to produce physical component summary and mental component summary without substantial loss of information (Ware et al. 1996; Jenkinson et al. 1997).

The SF12 has been tested for validity, reliability, responsiveness by its developers and by other authors for various conditions (Ware et al. 1996; Dunbar et al. 2001; Hurst et al. 1998; Gandek et al. 1998).

SF12 has been used widely for total knee replacement patients and like OKS has shown to have a higher completed questionnaire return compared to other generic health measures SF36, Nottingham Health Profile and Sickness Impact Profile with an average time of completion of 7.7 minutes (Dunbar et al. 2001).The total scores are shown as two meta scores, a physical component summary (PCS) and a mental component summary (MCS). The lowest score is 0, indicating worst possible health and the highest score is 100, indicating the best possible health.

5.4.7. Data Analysis

Data was screened for normality using the Shapiro-Wilk test. Tables showing normality tests for the study are given in Appendix I. Differences between the groups in patient demographics and pre-operative outcome measures were analyzed using t test and Fisher Exact tests. Both post-operative scores and the differences between pre-operative and follow-up scores were analyzed for any effects of BMI classification. Differences between pre-operative and follow-up scores (change scores) were calculated from absolute scores by subtracting the baseline scores from the scores at the two follow up

assessments. This means that for both OKS and SF12 components, a positive change score indicates an improved knee function and improved quality of life respectively. Between group comparisons of the pre and post-operative scores, which were not normally distributed were carried out using Mann Whitney U test (BMI group effect) and Friedman's ANOVA (time affect). Change scores which were normally distributed were analysed using independent t test to compare the improvement in outcome scores at six months and one year between the two BMI groups. A Bonferroni correction was applied for multiple comparisons.

Pearson's correlation coefficients between BMI and absolute and change scores were also calculated.

The level of significance was set at $p < 0.05$ for all statistical tests. All statistical analyses were carried out using SPSS version 19.0

5.5. Results

5.5.1. Baseline between group comparisons

The pre-operative patient characteristics of the two BMI groups were as shown in Table 8. The baseline data shown in the table is for a total of 171 (73 non-obese and 98 obese) cases for which complete baseline data was available. Complete OKS follow up data (both six months and on year) was available for 76 cases (31 non-obese and 45 obese) and complete SF 12 follow up data was available for 81 cases (36 non-obese and 45 obese). This indicates a high attrition rate of 56% and 53% for OKS and SF12 respectively.

As shown in Table 8, the obese group consisted of more females (48.0% vs. 69.7%, p=0.002). Further, more patients in the obese group suffered from hypertension (72.2 vs. 45.3%, p<0.001) and Diabetes Mellitus (18.3 vs. 6.6%, p=0.015).No statistically

significant difference was found for mean age between the two groups (65.0 years in obese patients vs. 65.7 years in non-obese patients, p = 0.089). . The Oxford Score at the pre-operative assessment was significantly lower, which means higher functional difficulties in the obese group compared the non-obese group (15.3±7.3 vs. 18.8± 8, p=0.003). Pre-operative SF12 components were not significantly different between the two groups.

Average duration of hospital stay was similar for both groups; 6.5 days vs. 6.7 days for the non-obese and obese group respectively.

5.5.2. Normality tests

Absolute scores of both OKS and SF12 were non-normally distributed, except pre-operative OKS score which was normally distributed. Change scores of both OKS and SF12 were normally distributed. Results of the tests for normality are listed in Appendix A.

Table 8 Mean (SD) of the demographics and number (%) of co-morbidities for the two BMI groups and the total sample. P-values of independent t test unless otherwise stated

Variable	Total sample (n= 171)	Non-obese (n = 73)	Obese (n = 98)	p
Age (years)	66.7 (8.7)	68.0 (8.8)	65.7(8.4)	0.089
BMI (kg/m^2)	31.4 (5.6)	26.6 (2.1))	35.0(4.7)	<0.001
Female n (%)¥	105 (60.3)	36 (48.0)	69(69.7)	0.002
R.A n (%)	11 (6.3)	5 (6.6)	6 (6.1)	0.24
OKS (pre) (0-48)	16.7 (7.8)	18.8 (8.0)	15.3 (7.3)	0.003
SF12 PCS (pre)	29.0 (6.7)	28.8(6.2)	30.0(7.0)	0.833
SF12 MCS (pre)	49.4 (11.6)	51.1(10.6)	48.3(12.1)	0.118
Diabetes Mellitus n (%)¥	23 (13.2)	5 (6.6)	18 (18.2)	0.015
Hypertension n (%)¥	96 (55.2)	34 (45.3)	72 (72.7)	<0.001
Respiratory dis. (%)	33 (18.9)	15 (20)	18 (18.2)	0.16
Cardiac disease n (%)¥	22 (12.6)	8 (10.7)	14 (14.1)	0.15
Vascular disease n (%)¥	11 (6.3)	4 (5.3)	10 (10.1)	0.12
Previous TKR n (%)¥	28 (16.1)	14 (18.6)	14 (14.1)	0.12
Previous THR n (%)¥	22 (12.6)	8 (10.6)	14 (14.1)	0.15

¥Fisher's exact test, RA=Rheumatoid Arthritis, PCS = physical component summary of the SF12, MCS = mental component summary of SF12

5.5.3. Within group comparison of absolute scores, time effect

The median and range of the absolute scores for the two BMI groups are given in Table 9. Physical function, as measured by OKS and the physical component of the SF12 showed significant improvement from pre-operative to both follow up assessments ($p < 0.001$). However, the mental component of the SF12 did not show any significant difference between the three assessment points ($p = 0.254$). For the OKS and the SF12 physical component the biggest improvement was seen from pre-surgery to 6 months with little or no change from 6 months to one year. This was the case for both BMI groups.

5.5.4. Between group comparison

Post-operative scores are given in Table 9. There were no statistically significant differences between the two groups in any of the post-operative outcome measures.

Table 9 Median (range) of the values of the outcome measures for the two BMI groups at 6 months and one year. Effect size, P-values of the group and time effect (pre surgery, 6 months and one year)

Variable	Non-obese (n=25)	Obese (n=39)	ES	P – value (group)	P-value (time)
OKS 6 months	32 (40)	34 (35)	0.09	0.711	< 0.001
OKS 1 year	36 (39)	36 (35)	-0.01	0.664	
SF12 PCS 6 months	35.8 (33.4)	34.5 (38.2)	-0.12	0.581	< 0.001
SF12 PCS 1 year	42.8 (33)	36.9 (36.7)	-0.44	0.091	
SF12 MCS 6 months	54.6 (44.2)	56.3 (42.1)	0.05	0.805	0.254
SF12 MCS 1 year	54.9 (43.9)	54.9 (40.5)	0.02	0.827	

PCS = physical component summary of the SF12, MCS = mental component summary of SF12

5.5.5. Between group comparison of change scores

The mean and standard deviations for change scores for the two BMI groups are given in Table 10. On comparison between groups using change in OKS scores, no significant difference was seen between the BMI groups for change in OKS from pre-operative to six months follow up or from pre-operative to one year follow up. Similarly no significant difference was observed between groups for change scores (pre-operative to six months post-operative or pre-operative to one year follow up) for both physical and mental component of SF12.

Table10 Mean (SD) of the change score data for the three BMI groups, Means and Standard deviations

Outcome	Non-obese (n=31)	Obese (n=45)	ES	p- value
OKS (6mo-pre)	12 (11.2)	15.9 (8.7)	0.4	0.096
OKS (1yr-pre)	14.1 (10.9)	16.8 (8.8)	0.28	0.229
SF12 PCS (pre-6mo)	7.9 (12.8)	6.8 (10.5)	-0.09	0.672
SF12 PCS (pre-1yr)	10.9 (11.9)	6.5 (8.3)	-0.44	0.063
SF12 MCS (pre-6mo)	0.56 (11.1)	2.8 (11.9)	0.19	0.389
SF12 MCS (pre-1yr)	0.74 (8.6)	2.8 (10.9)	0.21	0.370

PCS = physical component summary of the SF12, MCS = mental component summary of SF12

5.5.6. Correlations between outcomes and BMI

Table 11 shows the strength of the relationship between the outcome measures and BMI value. Observing the relation between BMI and OKS, only the relationship between pre-operative OKS and BMI showed a weak but statistically significant correlation ($r = -0.255$, $p<0.05$).Thus indicating a lower score and hence more functional difficulty with increasing BMI value, pre operatively. On observing the relation between BMI and SF12 scores, weak but statistically significant relation was seen between BMI and one year PCS scores ($r = -0.270$, $p = 0.015$) and between BMI and change score at one year ($r = -0.228$, $p = 0.041$). The negative relation between BMI and PCS change score indicates that those with higher BMI improved less in their overall physical health quality of life.

Fig 1, 2 and 3 show scatter diagrams of the outcomes which showed the strongest relationship with BMI; pre-operative OKS ($r= -0.255$), the physical component of the

SF12 at one year (r= -0.270) and the change in physical component score from baseline to one year (r= -0.228).

Table 11 Pearson's correlation coefficients between BMI and the outcome measures before surgery, at 6 months and 1 year after surgery and between BMI and the change scores

	OKS - BMI	PCS - BMI	MCS – BMI
Pre-operative	-0.255*	-0.071	-0.047
6 months	-0.039	-0.098	-0.004
1 year	-0.103	-0.270*	-0.060
6 months – Pre	0.157	-0.040	0.043
1 year – Pre	0.093	-0.228*	-0.004

* Significant at $p<0.05$ PCS = physical component summary of the SF12, MCS = mental component summary of SF12

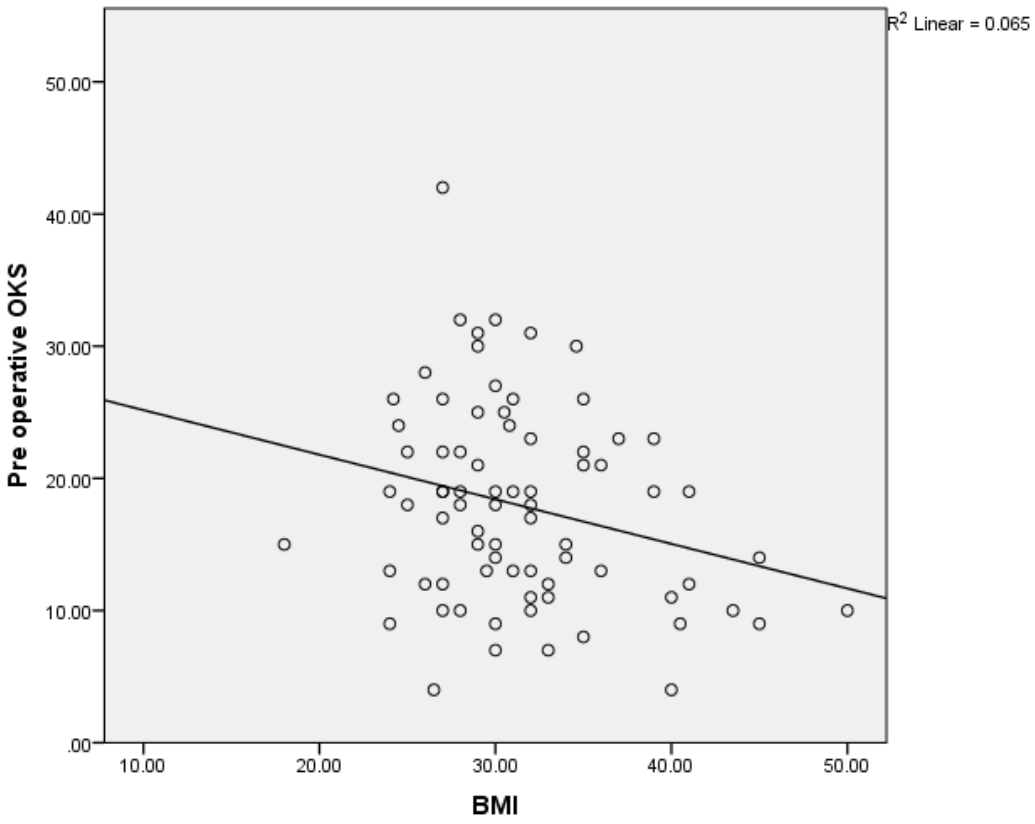

Figure 1 Scatter plot showing relationship between BMI (kg/m2) and pre-operative OKS

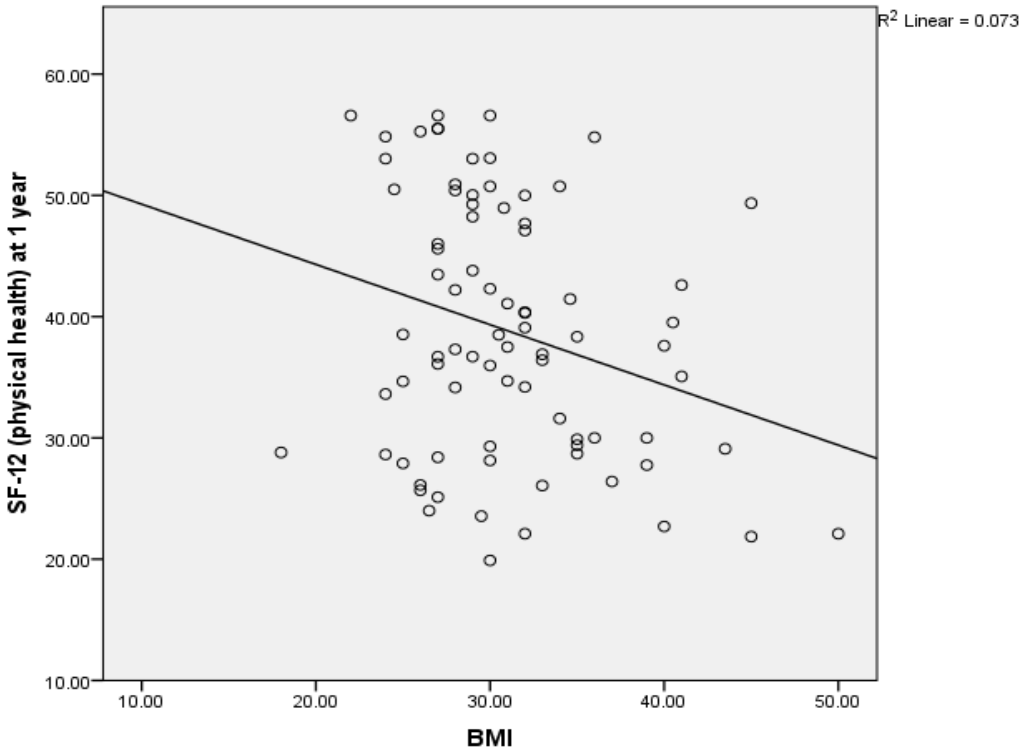

Figure 2 Scatter plot showing relationship between BMI (kg/m2) and SF12 (PCS) at one year post surgery

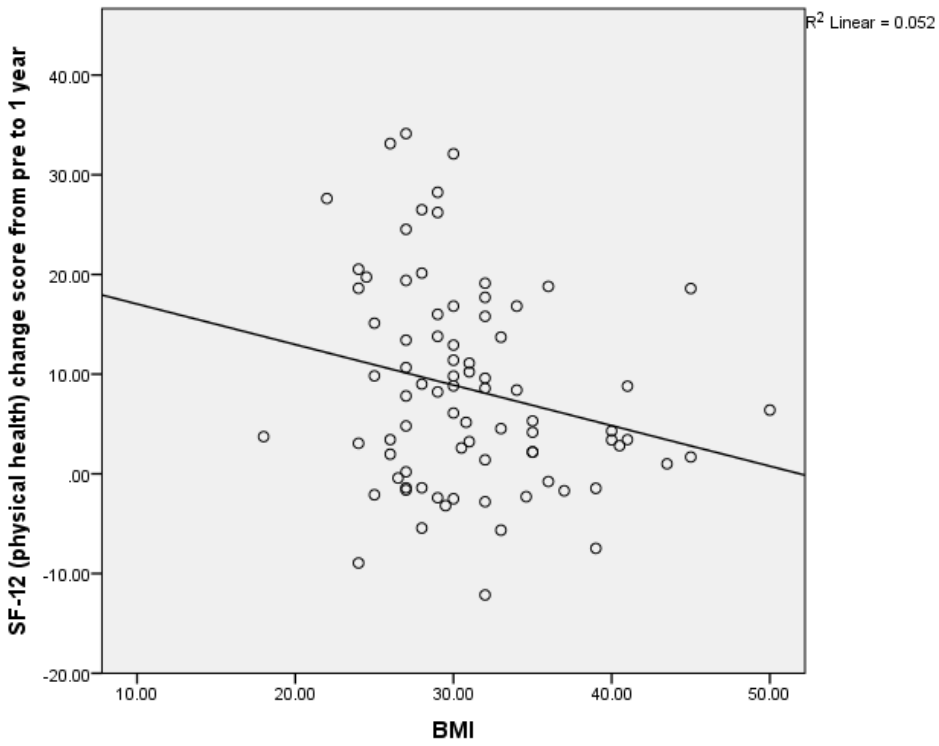

Figure 3 Scatter plot showing relationship between BMI (kg/m2) and SF12 (PCS) change score from pre-operatively to one year post surgery

5.5.7. Complications and revisions

A total of 16 patients had a local complication (wound infection or wound leak) post-surgery, of which, 5 (6.7%) were from the non-obese, 11 (11%) were from the obese group (Table 12). A total of 18 patients had a post-operative systemic complication of which 6 (8%) were from non-obese, 12 (12%) from the obese group. A total of 6 (3.5%) patients underwent revision surgery post primary total knee replacement of which 2 (3%) were in the non-obese, and 3 (3%) in the obese group. The rate of above complications and revision were not statistically significantly different between the two groups.

Table 12 Number (%) of post-operative complications and revisions in BMI groups

	Non-obese (n=73)	Obese (n=98)	p- value
Local complications	5 (6.7%)	11(11%)	0.13
Systemic complications	6 (8%)	12 (12%)	0.14
Revisions	2 (3%)	3 (3%)	0.30

5.6. Discussion

5.6.1. Summary of findings

The null hypothesis of the study that BMI has no effect on outcomes was accepted as it was found that at short term (up to one year post surgery), the patient perceived benefits of total knee replacement was not different among two groups with different BMI.

It has been reported that most improvement in function after total knee replacement occurs up to 26 weeks after which little improvement is gained (Kennedy et al. 2008). The same was seen for this study sample, with improvement in knee related function from the pre-operative state to post-operative state (six months and one year) significant in all BMI groups of the study, while, there was little change in knee function from six months postoperatively to one year post-operatively. This again, was true for both BMI groups.

The analysis of the self-report measures was carried out with both the absolute scores and the change scores. While the pre-operative absolute score for knee function was poorer for the obese compared to the other group, no significant difference was found in the six month and one year post-operative scores between the two groups. The change in knee function and quality of life from pre to six month and one year post surgery which was analyzed using change scores was also not significantly different between the groups. A lower pre-operative but comparable post-operative knee function scores and comparable change in knee function would imply that though pre-operative knee function was statistically significantly lower in obese, the difference was not large enough to affect the post-operative knee function or improvement in knee function.

Correlation analysis both, numerically and as shown graphically in the scatter diagram indicated no or weak relationships between BMI values and both post-operative scores and change scores. Even though statistically significant, the relation between BMI and overall physical function at one year was weak ($r = 0.27$) and that between BMI and change in overall physical health from pre-operatively to 1 year after surgery ($r = 0.23$) was also weak. Moreover, scatter plot for the relation between these variables does not indicate a clear association, with the values largely scattered across the 25 kg/m^2 to 35 kg/m^2 values of BMI. However, few extreme values indicating high BMI and low outcomes score (four in Figure 2) could have resulted in the in a statistically significant correlation.

Finally, the rate of complications and revisions were not statistically significant between the two BMI groups. Therefore, the current study findings indicate similar degrees of

benefits as quantified by the OKS and SF12, complications and revision rates from the surgery irrespective of patient BMI group.

5.6.2. Comparison of results with previous evidence

In terms of differences between groups, the findings of our study are consistent with that of majority of the other studies investigating the effect of BMI on WOMAC (Stickles et al. 2001; Bourne et al. 2007; Nunez et al. 2011). Nunez et al. (2010), defining their BMI categories as those with a BMI ≥35 kg/m^2 (n = 60) for severely obese and those with a BMI < 35 kg/m^2 (n = 60) as the control group observed similar significant improvement in both groups for the total WOMAC at 12 months post operation. A larger study by Stickles et al. (2001) saw no significant difference in change scores for WOMAC between their five BMI groups (BMI <25kg/m^2, n = 146, BMI = 25-29kg/m^2, n = 304, BMI = 30-35kg/m^2, n = 271, BMI = 35-39kg/m^2, n = 149, BMI ≥ 40kg/m^2, n = 92) at one year follow up. In a separate rating of stair ascending and descending difficulty and satisfaction with surgery, Stickles et al. (2001), however conclude that despite finding greater difficulty with stairs, obese patients were as satisfied with the results of the surgery as other patients.

Even at longer follow up of 5 -11 years, no difference in the improvement in WOMAC scores between BMI groups (BMI <25kg/m^2, BMI = 25-30kg/m^2, BMI = 30-35kg/m^2, BMI = 35-40kg/m^2, BMI > 40kg/m^2) has been found (Bourne et al. 2007). Contrary to these findings, Hawker et al. (1998) in a community based study found that though BMI was not a significant predictor of pain; higher BMI was associated with worse physical function on the WOMAC at 2-7 years after surgery in 2 of their 3 stratified samples (p = 0.02 and p = 0.01).

The conflicting results in studies with longer term follow up is further seen in studies assessing investigator measured outcomes such as the Knee Society Score (KSS). KSS and radiographic outcomes were not found to be statistically different between obese (BMI ≥ 30kg/m^2) and non-obese (BMI < 30kg/m^2) at a follow up ranging from 5 - 6 years (Spicer et al. 2001; Amin et al. 2006a). In contrast, other mid-term to long term

studies have observed a poorer outcome in obese (BMI $\geq$ 30kg/m^2) (Griffin et al. 1998; Foran et al. 2004a; Foran et al. 2004b).

Change in quality of life as from pre-operative state to six months and one year after TKA as assessed by the physical and mental component score of SF12 in this study, was also similar in all BMI groups in our study. Other studies using SF36 (Stickles et al. 2001) and SF12 (Dowsey et al. 2010) also saw no effect of BMI (greater than or less than 30 kg/m^2) on change or improvement in quality of life. The correlation analysis in this study however revealed a significant negative correlation between BMI and PCS scores of SF12. As mentioned above in section 5.6 (i), the relationship was not clear in the BMI range of 25-35 kg/m^2 and though the relationship was weak, few values at the higher end of BMI ($\geq$ 40 kg/m^2) resulted in a statistically significant pull to a negative relation. A negative correlation of BMI with overall physical health (PCS of SF36) at one year after TKA (PCS of SF36) was also seen by Stickles et al. (2001). Dowsey et al. (2010) did not find significant differences between their obese and non-obese group for PCS score at one year but did see significantly lower PCS in morbidly obese. Therefore, some effect of higher BMI on overall physical function is implied from these findings, although, the BMI after which overall physical health declines cannot be concluded form the study. A significantly higher number of patients with comorbidity such as type II diabetes and hypertension in the obese group in the current study could have affected the overall physical health at one year after TKA

5.6.3. BMI and TKA outcomes

Apart from the association of BMI with the overall physical function as seen in the current study, the literature review (Chapter 4) indicates a poorer function scores in other studies particularly in relation to activities such as stair climbing and descending. The suggested reason for this is the increased load the knee joint has to bear in obese patients and therefore greater joint stressed and muscular work could result in pain and difficulty during these activities. However, knee function in this study was not affected by BMI.

The assumption of increased stresses on the joint due to obesity is also enforced by the association of obesity as a causative factor of the progression of knee osteoarthritis towards symptomatic end stage osteoarthritis requiring a TKA (discussed previously in Chapter 3). There is consistent evidence that there is a positive link between weight/body mass and end stage knee osteoarthritis.

Obesity, strictly, is defined as accumulation of body fat (Prentice and Jebb 2001). Applying this differentiation of body composition to the above conclusion, obesity defined as increased adipose mass would add to the body mass causing the mechanical effects stated above on the joint. However, a purely mechanical effect of body mass causing the joint disease does not clarify the stronger association of obesity with OA in women, that all obese persons do not suffer from OA, similar strength of association of obesity and OA is not seen with all weight bearing joints and the evidence of association of obesity with non-weight bearing joints such as joints of the hand. Mechanical effect of obesity has been proposed to cause poorer functional outcomes after TKA in obese. The assumption of a negative effect of obesity as measured by BMI on the premise of increased mechanical loading and therefore greater functional difficulty in obese patients by virtue of their higher body mass is also not supported by this study. Moreover, the conflicting results in the literature are again not clarified by the sole effect of a mechanical nature on the joint by obesity.

Aging is associated with both increase in body fat and decrease in the muscle mass which implies decreased muscular support at the joint to maintain its stability (Messier et al. 1994). In addition, there is a known association of adiposity and disability and poor health outcomes (Ramsay et al. 2006). Body mass index being the most commonly used measurement of obesity in the study of obesity and knee osteoarthritis and the only method used for defining obesity in the study of outcomes after TKA, though gives evidence of the effects of body mass on the joint in some studies, its limitation in not differentiating fat and lean mass does not allow it to clarify the above effects of adipose tissue and muscle tissue. The distribution of fat has been suggested to play a role in this mechanical effect of obesity. While trunkal fat has effect on hip and knee joint, the hip and thigh fat has its effect on knee and little on the hip (Sturmer et al. 2000). The effect of

regional distribution of fat on the knee is again unclear with BMI as a measure of obesity. For a better understanding of the effect of true obesity on total knee replacement outcomes, it would therefore be justified and worthwhile to explore the use of other body composition measurement methods in addition to BMI in understanding the influence of obesity in the TKA population.

5.7. Chapter Summary

With the increasing prevalence of obese patients in the TKA population, it is important to establish if these patients have results comparable with non-obese TKA or have to live with compromised results after surgery. This chapter presented a retrospective study assessing the effect of BMI on patients' perception of their outcomes which are important in clinical decision making as patients' concerns and priorities may be different from that assessed by health providers. The findings indicated that the patients perceived improvement in function and quality of life is not different between BMI groups based on a cut-off point of 30 kg/m^2. However a negative effect of BMI used as continuous data was observed on overall physical function one year after TKA. The above retrospective study has been accepted for publication as a journal article in the journal titled 'Arthritis'. Copy of the accepted manuscript has been attached in Appendix E.

CHAPTER 6: A PROSPECTIVE STUDY OF THE EFFECT OF BODY COMPOSITION ON TKA OUTCOMES: STUDY METHODS

6.1. Chapter overview

This chapter presents the protocol used to assess the effect of body composition on patient reported outcomes for up to one year following TKA. The chapter begins with an introduction to the study and its aim. The choice of methodological approach for the study has been justified followed by a description of the study procedures. Methods of assessment of body composition and outcomes measured in the study are then described. Finally, the methods used to extract and analyse the measured data have been described.

6.2. Introduction

The results and conclusions from the literature show a lack of uniformity regarding the effects of BMI of total knee replacement outcomes, thus, making it difficult to suggest a cut off point for clinical obesity which may be the critical point which predisposes to complications of failed outcome. While a poorer outcomes on obese patients is expected due to increased stress on prosthesis and association of obesity with other comorbidity, the previously discussed retrospective study and other studies evaluating the effect of BMI on TKA outcomes do not show any difference between obese and non-obese groups in terms of functional gains. Obesity is defined as excess accumulation of fat in the body. Body mass index as a measure of obesity though widely used has its limitations in measurement of obesity and its distribution. To understand the true effect of obesity on the outcomes of TKA and the underlying mechanisms through which obesity may or may

not affect outcomes after TKA, this study explores the effect obesity measured by other clinically viable body composition methods including Bioelectrical Impedance Analysis (BIA) of body fat percentage, ultrasonographic measurement of regional fat, waist circumference and waist to hip ratio in addition to BMI on the outcomes following TKA.

6.3. Aim of the study

The study aims to assess the effect of body composition as measured by Bioelectrical Impedance Analysis (BIA) of body fat percentage, ultrasonography measurement of regional fat, waist circumference, waist to hip ratio and BMI on the patient-reported outcomes for up to one year following TKA.

6.4. Methodological approach

Randomised controlled trials (RCT) are considered the gold standard for testing hypothesis (Mann 2003; Thadhani and Tonelli 2006). However, in some areas of research, observational studies are more suitable or even viable than RCT. Research assessing the association of obesity with TKA requires an observational design as patients cannot be randomised into obese and non-obese group. A prospective cohort study as that used in this study has been described by Grimes and Schulz (2002) as *'…the experience of a group exposed to some factor with another group not exposed to the factor. If the former group has a higher or lower frequency of an outcome than the unexposed then an association between the exposure and outcome is evident'.* The 'exposure' described here is obesity in this study.

One of the main advantages of an observational design is that it does not interfere with patient or surgeon choices. Observing a broader range of patients without rigorous controlled conditions would be more representative of clinical practice and thus add to study relevance i.e., whether the study results can be applied to common clinical situations.

The relevance of the study to practice is also influenced by specifics such as the treatment implementation, adequate reporting of patient characteristics and appropriate choice of outcomes measures (Hartz and Marsh 2003).Cohort studies can also be advantageous in investigating *potential* multiple outcomes resulting from the exposure, however, while testing of the association of exposure with many outcomes, misleading interpretation can arise if only significant results are reported (Grimes and Schulz 2002). Therefore it is suggested that primary and secondary outcomes to be examine should be planned beforehand as has been done for the current study. Another important consideration is the sufficient time period between the measurement of exposure and outcomes to occur or change. It has been reported that the greatest improvement in the functional recovery after TKA occurs in the first 12 weeks after surgery which then continues up to 26 weeks (Kennedy et al. 2008). Assessment of patient reported outcomes after TKA have been reported to have shown significant improvement at two and four months compared to the pre-operative status (Parent and Moffet 2002). Therefore, a follow up of one year in this study would allow sufficient time to assess the effect of obesity on immediate surgical outcomes and also the patient perceived functional outcomes.

Bias or systematic error is one of the main threats to the internal validity of an observational study such as the current study. A bias due to dissimilarity between the exposed and the non-exposed groups other than the exposure itself reduces the comparability of the groups (Grimes and Schulz 2002). Alternatively, a bias can also occur when follow up information is less likely to be collected from patients who have a worse outcome, as had been observed when using patient reported outcomes in TKA patients (Kim et al. 2004). As opposed to bias, confounding (a third variable which affects outcome) can be corrected before or after the study to achieve homogeneity of between groups and has been attempted in this study by using appropriate statistical

models. Bias and confounding which affected this study has been detailed as study limitations in Chapter 9.

6.5. Study procedures

6.5.1 Ethics

Approval for this research study was obtained from the NHS Lothian Research Ethics Committee. Main ethical issue presented to the committee was the careful wording of the participant information sheet to ensure sensitivity towards participants' body image and create no misunderstanding of their perception of their body weight and outcomes of their forthcoming surgery. The information sheet was approved by the ethics committee. Appendix C contain copies of participant information sheet and patient consent forms that pertain to this study.

6.5.2. Participants

All patients under the care of six surgeons undergoing elective primary TKA at the Royal Infirmary of Edinburgh were eligible to participate, provided they did not have the following exclusion criteria:

a. Infective arthritis
b. Minimally invasive total knee replacement
c. Simultaneous bilateral total knee replacement
d. Neurological or cognitive impairments affecting movement or understanding of instruction/ questionnaires.
e. Inability to give informed consent

Patients with neurological/ cognitive impairments or inability to give informed consent were excluded due to ethical issues. The other exclusion criteria were followed because of their influence on the outcomes. Other factors such as age, previous hip or contra lateral knee surgeries were not excluded so that the sample was as representative of the TKA population as possible. Patient with surgically fitted devices such as pacemakers were excluded from BIA measurements.

Potential participants were identified from the patients on the waiting list for TKA. Patient list of six surgeons (of the Orthopedic Department, Royal Infirmary of Edinburgh) were included for recruitment. Potential participants were sent letters of invitation for the study and participant information sheet with the contact details of the researcher by post. Consenting participants were then contacted by the researcher by phone or e-mail and recruited prior to their pre admission clinic appointment. Participants were assessed pre-operatively (baseline) at the time of their pre admission. The pre-operative assessments were carried out at the Clinical Research Facility at the Royal Infirmary of Edinburgh, on the same day as the patients' pre admission clinic appointment. For the post-operative assessment, the questionnaires were sent to the patients address via post at six weeks after surgery. Further follow up questionnaire data for six months and one year after surgery was obtained from the hospital database.

6.5.3. Pre-operative assessments

The baseline (pre-operative) assessment included (details in the following sections):

a. BMI: weight and height of the participant was measured from which BMI was calculated as body mass (kg) divided by the height squared (m^2).
b. Waist to hip Ratio: with the patient in standing, the waist and hip girth was measured using a measure tape and the ratio was calculated as waist circumference divided by the hip circumference.
c. Ultrasonography: with the participant supine, the subcutaneous fat thickness above the knee undergoing total knee replacement was measured. Inter and intra-rater

reliability tests of the ultrasound measurement protocol were conducted before the commencement of the current study.

d. Bioelectrical impedance analysis: with the participant supine, the multi segmental and multi frequency analyzer was used to assess body composition. Intra-rater reliability test of the BIA measurement protocol was conducted before the commencement of the current study.
e. Comorbidity: Medical records of the participants were reviewed to note comorbidity present and history of previous surgeries.
f. Patient characteristics: age, gender, date of birth, laterality, previous knee replacement, and hip replacements were noted.
g. The primary outcomes measure, Oxford Knee Score, which is a self-report questionnaire, was completed by the participant at the baseline assessment.
h. Secondary outcomes measures Short Form 12 questionnaire and the Visual Analogue Scales were completed by the patient at the baseline assessment.

6.5.4. Surgery

All participants received elective surgery and the post-operative care via the integrated care pathway used at the Royal Infirmary of Edinburgh. Each patient's operation note was reviewed to note the surgical approach and the type of implant. Any complication during the hospital stay, number of days of hospital stay and any complications post discharge were noted from the patient medical records.

6.5.5. Post-operative assessments

The follow up (post-operative) assessments included:

a. Oxford Knee Score, SF12 and the Visual Analogue Scale were posted to the patients at six weeks after their surgery. These were completed by the participants and sent back to the researcher.

b. Six month and one year follow up OKS and SF12 data were obtained from the hospital database
c. Post-operative complications: post-operative patient charts were reviewed to record any local and systemic complications.
d. Referral for revision surgery: follow up notes were reviewed to note if the participant has been referred for a revision surgery during the period of the study.

6.6. Measurement of body composition

6.6.1. Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) is a widely used method by clinicians and researchers to determine body composition. The theory behind bioelectrical impedance analysis is based on the relationship between the impedance and water content of the body. A small electric current (of approximately 0.8mA) is introduced into the body via electrodes which generates voltage between different points in the body (Kyle et al. 2004). The actual parameter which is measured by the BIA is the impedance which is given as the ratio of voltage upon the current. The total body water is then estimated from this measured electrical impedance of body tissues using established equations.

The multiple frequency BIA uses different frequencies (0,1,5,50,100,200 to 500 kHz) of current to measure Total body water (TBW), (intra cellular water (ICW), extracellular water (ECW) and fat free mass (FFM).

Machine specifications

Maltron Bioscan 920-2 (Maltron International Ltd, Essex, U.K.) was used for bioelectrical impedance analysis. The Maltron Bioscan Analyser is portable and non-

invasive equipment. It is a multi-frequency analyser testing impedance at frequencies of 5 kHz, 50 kHz, 100 kHz, and 200 kHz.

The hardware components of the analyser consists of the Bioscan 920-2 analyser, ME4000 disposable electrode pads, MEC1106-2 set of electrode cables. The Maltron USB software for Windows and XP and Maltron data export software was used to import all the data from the analyser. Regular calibrations (twice a week) of the analyser were performed using the MCR 1205 Calibration test rig, provided by the manufacturers.

Standardisation of testing conditions

Standardisation of BIA testing condition was developed according to the manufacturer's guidelines and the ESPEN (The European Society for Clinical Nutrition and Metabolism) guidelines. The measurement conditions for the participants were standardised as follows:

a. All participants' weight and height were measured in kilograms and millimeters respectively. This was done at the time of the BIA measurement.
b. Standardised hydration conditions for participants: No alcohol consumption up to 24 hours prior to testing, no exercise up to 24 hours prior to testing, testing at least 2-3 hours after a meal and no consumption of large amount of water prior to testing.
c. Site of electrodes on the body were checked to make sure there were no skin lesions. The area was then cleaned with alcohol.
d. Testing was done with patients' supine with limbs abducted. Arms were separated from the trunk by approximately 30 degrees and the legs were separated by about 45 degrees. In patients with greater thigh/arm circumference, skin between thighs/arms was separated using a blanket.
e. No contact with the metal frame of the bed.
f. Assessment room free of strong electrical or magnetic fields.
g. BIA measurements were not done in patients fitted with a pacemaker.

The hydration conditions for participants were listed on the participant information sheet and were reminded to the participants at the time of confirmation of appointment.

Procedure for measurement

Patient height in millimetres and weight in kilograms were measured. BIA measurements were done with patients in supine. Areas of electrode placement were tested for skin lesions. Before placing the electrode pads, the area of the skin was cleaned with alcohol. Once the adhesive electrode pads were firmly placed (Figure 4), the numbered electrode cables were clipped to the corresponding location on the body. With the electrodes in place and the patient resting in supine, patient data including the measured height, weight, age, sex, ethnic group were entered into the analyser. A '5 segment' option was chosen for the BIA measurements. The parameter calculated by the machine including BMI, whole body fat mass, fat percentage (BF %) was noted into the data collection sheet.

Once data was collected these were uploaded into the computer using the Maltron USB software for Windows and XP.

Figure 4 Electrode placements for BIA measurement

6.6.2. Ultrasonography

Ultrasonography is a non-invasive method of imaging anatomy. It consists of the ultrasound scanner instrument with display screen and ultrasound probe or the transducer. The ultrasound transducer (or probe) generates ultrasound waves which are sent into the body tissues. These ultrasound waves produce 'echoes' which are reflected back from the body tissues into the transducer The ultrasound echoes are reflected at boundaries or interfaces of tissues with different acoustic properties. These reflected echoes are then processed by the ultrasound instrument and displayed as dots which form the anatomic image (Kremkau 2001).

Machine specifications

The ultrasound imaging system consists of the following components: Sonosite ultrasound system, C60/5-2 MHz 60-mm curved array transducer, Ultrasonic coupling gel and Sitelink image manager software.

Procedure for measurement

Measurements were taken from the affected side with the participant supine. A single copper wire was attached perpendicular to the probe with a tape. This copper wire displays a thin shadow on the ultrasound image which helps to identify the centre of the probe in the image and also to make the corresponding markings for structures on the skin.

Once participant information was entered into the machine, live imaging mode was used to image the tissues. The ultrasound coupling gel was applied on the probe to allow for ultrasound transmission into the body tissue.

With the knee extended, and the probe parallel to the femur, an image was obtained of the lateral femoral epicondyle. To identify the lateral epicondyle of femur, the probe was placed on lower thigh (lateral side) and then moved down to the outer (lateral) side of the

knee till sharp bony curvature was seen. The highest point of the bony curvature was then marked as the lateral epicondyle of femur. Similarly, the medial femoral epicondyle was marked. For this, the probe was placed on the medial side of lower thigh and then moved down to the inner (medial) side of the knee and the highest bony curvature was marked on the skin as the medial femoral epicondyle.

The knee calliper was then used to measure the distance between the medial and lateral femoral epicondyles. The mid-point of the distance between the epicondyles was marked on the knee anteriorly. Using a measure tape, a distance 7 cm proximal to this mid-point, on the anterior aspect of the thigh was marked. This site was used for imaging regional fat thickness. To relax the anterior muscles of the thigh, the knee was put in a position of slight flexion (maximum 40 degrees) using pillows for support. This point on the anterior aspect of the knee was then imaged in the sagittal plane. Imaging was done with the probe parallel to the length of the femur. Once imaging was completed, gel from the participant's skin and from the ultrasound probe was removed. The skin area and probe surface was cleaned with a disinfectant spray. Using the measurement callipers on the ultrasound instrument, the depth of the tissue lying between the lower layer of the skin and the upper layer of the muscle tissue was measured. This layer contains the fat deposits. The distance from the lower end of the skin to the top layer of the quadriceps muscle, was measured and noted at 25%, 50% and 75% distance from the left of the screen. The measurements were noted in the data collection sheet.

Images were uploaded using the Sonosite software and measurements were further analyzed using imaging software (Image J, NIH, Bethesda Maryland).

6.6.3. Waist to hip ratio and waist circumference

Waist to hip ratio (WHR) is essentially the waist circumference divided by the circumference of the hips. This is a commonly used method to distinguish central fat distribution from peripheral distribution. Waist circumference and WHR are significantly related to the actual anatomical distribution of adipose mass and volume as measured by cadaver assessment (Martin et al.2003). Predominant central adiposity is considered a

strong risk factor cardio-vascular disease, hypertension, stroke, diabetes mellitus (Donahue et al. 1987) therefore a large waist circumference is also seen to predict greater morbidity. On the other hand hip circumference is suggested to be inversely associated with morbidity suggesting that lesser the hip circumference greater is the risk of morbidity (Snijder et al. 2006). Thus a large waist to hip ratio which might be due to a large waist circumference or a smaller hip circumference predicts greater health risks. One of the features of WHR is that it is partially independent of total adiposity and for a given value of WHR there may be variability in the total body adiposity thus it is a measure of the distribution and not total fat levels. Moreover, increases in adiposity including abdominal adiposity may not be detected by WHR if there is an increase in the hip circumference along with the waist circumference.

Though a standardised site for the measurement of the waist circumference has not been established, the WHO (2008) recommends that waist circumference should be measured at the mid-point of the lower border of the lower rib and the upper border of the iliac crest. The hip circumference according to the WHO (2008) recommendation is to be measured around the widest portion over the buttocks.

Standardisation and procedure

During measurement, the patients were to stand with their outer garments off and breathe normally. Waist circumference was measured at a site mid-point between the lower rib and the upper part of the iliac crest. Hip circumference was measure around the widest portion of the buttocks as recommended by WHO (2008). All measurements were done with a single non stretchable measure tape.

6.6.4. Body Mass Index

Body Mass Index (BMI) is calculated as the body mass in kilograms divided by height in meters, squared. BMI, also known as the Quetlet index was developed in the mid-19th century on the basis of the observation that body weight is directly proportional to height in individuals with a normal frame (Romero-Corral 2008). It has been widely used as a measure of obesity in epidemiological studies. BMI has shown to have an association with percentage body fat and it is assumed that increase in body fat is usually accompanied with increase in weight. Therefore, it is widely used in research and clinical practice enabling a quick and inexpensive method for prediction of health risks from BMI defined obesity levels. Most health guidelines including the WHO (2000) define 'overweight' as BMI of 25.0 to 29.9 kg/m^2 and BMI greater than 30 kg/m^2 as 'obese'. However, BMI does not distinguish fat from fat free mass and thus can lead to misinterpretation of total fat content (Snijder et al. 2006; Khaodiar and Blackburn 2001; Rothman 2008). Therefore in some cases, for example in athletes, have a very low fat mass but by BMI classification may still fall in the overweight or even obese category because of their high muscle (lean) mass. Moreover in elderly due to decrease in height, BMI tends to be overestimated (Snijder et al. 2006) and it has been seen that for a given BMI, older persons have greater body fat compared to a younger adult (Gallagher et al. 1996). Despite these limitations, BMI greater than 30 kg/m^2 shows excellent specificity and positive predictive value for diagnosing obesity measured as body fat percentage (Romero-Corral 2008). Moreover, the simplicity of the measurement makes it a preferred method in large epidemiological studies examining obesity and its effects or in clinical practice when systematic and repeated collection of a measure of obesity is required (Frankenfield et al. 2001 Snijder et al. 2006)

Standardisation and procedure

Before measuring weight and height, participants were asked to remove shoes and heavy outer clothing. Weight of the participant was measured in kilograms on a weighing scale

and the height of the participant was measured in millimetres using a standiometer. The same weighing scale and standiometer was used for all participants.

6.7. Ultrasound protocol reliability

Protocols described for body composition methods of BMI, WC, WHR and BIA have been previously established in the literature as valid and reliable (Section 3.5, Chapter 3). However, measurement protocol for the measurement of subcutaneous fat thickness above the knee as described in section 6.6.2 above has not been previously used in this context. Therefore in order to assess if the given protocol is reliable, the inter-rater reliability and intra-rater reliability of fat thickness measurements using the described ultrasound protocol were evaluated and are described in the sections below.

6.7.1. Introduction

Currently the most commonly used methods for measuring subcutaneous fat thickness are those using skin fold callipers and ultrasonography (US). Because of the limitations of the skinfold method, ultrasonography was proposed as an alternative to skinfold measurement. Compared to the skinfold technique, the ultrasonography method offers the advantages of avoiding tissue compression, no requirement for palpation of muscle tissue interface and is potentially a more valid measurement in obese subjects for whom skinfold measurement are often problematic.

Early studies validating A- mode ultrasound with direct measurements such as needle puncture and electrical conduction saw high correlation between the subcutaneous fat thickness measurements by these direct measures and that by ultrasonography (Bullen et al. 1965, Booth et al. 1966). Quantification of subcutaneous tissue is now done commonly with the B- mode ultrasounds which have shown no significant differences in fat thickness measurement when evaluated against direct cadaver analysis (Maud and Foster 2006). In one study in morbidly obese persons (before gastric banding) and obese (after gastric banding), ultrasonography measurements of subcutaneous fat thickness was

shown to have a good correlation with that measured by CT scans, r = 0.78 and r = 0.72 respectively (Pontiroli et al. 2002).

Various studies have assessed reliability and reproducibility of US fat thickness measurement. Inter and intra-observer reliability assessment of US at 14 sites by Ishida et al. (1992) reported high reliability of US, their coefficient of inter observer variation (CV%) greater than 90% for 11 of the 14 sites measured for fat thickness. This high reliability was also confirmed by Bellisari et al. (1993) who observed CV% of 98% and 94% for intra observer and inter observer reliability respectively.

Although data show a reasonably high reliability and validity of US subcutaneous fat thickness measurement, there still exists some difficulties which affect measurement such as the pressure on the probe at the scan site which if not uniform and constant, may affect adipose tissue distribution and the standardisation of the scan site. Therefore, before applying the US technique on TKA patients in the prospective study, reliability of the measurements taken by the investigator were assessed.

6.7.2. Aims

The aims of the study were:

1. Test the inter-rater reliability of measurement of fat thickness above the knee joint using ultrasound technique.
2. Test the intra-rater reliability of measurement of fat thickness above the knee joint using ultrasound technique.

6.7.3. Method

Participants

The reliability testing involved participants from a pool of apparently healthy students and staff from Queen Margaret University, post TKA patients and members of a local weight loss group (Scottish Slimmers, Musselburgh) in order to test a wider range of body compositions. Individuals with injury or skin condition (e.g. active inflammation of the skin at the site of testing) which could interfere with the use of ultrasound probe were excluded from the study.

Investigators

The first investigator (VA) is also the principal investigator of the prospective study and therefore took part in both inter and intra rater reliability studies. Both the first (VA) and the second investigator (KJ) are physiotherapists with experience in musculoskeletal ultrasonography.

Assessment Procedure

Measurement of fat thickness above the knee joint using ultrasound technique was identical to that described in section 6.6.2

Height and body mass of the participants were also measured and BMI was calculated. Height of the participants was measured in millimeters using a stadiometer and body mass was measured in kilograms using a calibrated weigh scale.

Assessment protocol

To test intra-rater reliability, participants were tested by the first investigator (VA) twice (Scan day 1 and Scan day 2) with a minimum interval of 48 hours between assessments, to check for the intra-rater reliability. For inter-rater reliability, both investigators measured each subject on the same day with a 15 minute interval between the measurements (Scan VA and Scan KJ).

Data upload and analysis for all measurement were done by VA according to the methods described below.

Data Extraction and Analysis

Reliability assessments were all conducted at the Queen Margaret University, after obtaining ethical approval from the Queen Margaret University Research Ethics Committee.

Images from the ultrasound machine were further analysed and measured on imaging software (Image J, NIH, Bethesda Maryland). The average of the distance between the lower surface of the skin and the top layer of quadriceps muscle were calculated as the average of these distances at 25%, 50% and 75% distance from the left of the image.

Following standard normality distribution checks descriptive analysis of data was conducted (to provide mean and standard deviations of the measurements. Inter rater reliability was assessed using intra class correlation coefficient (ICC 3, 1) equation based on a two way analysis of variance (ANOVA) as described by Shrout and Fleiss (1979). Intra rater reliability was assessed using ICC equation (1, 2) described in another study which assessed appropriate statistical analyses for ultrasound reliability and had an identical between day scan repeatability design (Rankin and Stokes 1998). This equation ICC (1, 2) is equivalent to ICC (1, k) described by Shrout and Fleiss (1979) where k is the number of measurements (2 measurements for 2 days) instead of number of raters. Intra class correlation coefficient range from zero to one with the closer the value to one, greater is the assumed reliability. There is no universal standard for categorizing scores,

Nunnaly and Bernstein (1994) note that the effect of measurement error is minimal with ICC values greater than 0.80 while Chinn (1991) recommend an ICC of at least 0.60 for the measurement to be useful.

As ICC's give no indication of the magnitude of agreement between the ultrasound measurements (between day scans or between raters), Bland and Altman's methods to calculate the limits of agreement were employed (Bland and Altman 1986). A graph was plotted (Bland and Altman plot) between the relation between the size of the differences and size of the means. The Bland and Altman method calculates the bias which was estimated by the mean difference and standard deviation. The 95% limits of agreement were calculated as mean difference ± two times standard deviation. All statistical analyses were carried out using SPSS version 19.0.

6.7.4 Results

Participant characteristics

Participant characteristics of age, gender, weight, height, BMI and mean of the absolute differences are shown in Table 13.

Table 13 Sample characteristics (means ±SD and range)of the participants in the reliability studies

	Intra rater reliability sample		**Inter rater reliability sample**
N	20		13
Age [Range]	42.9 (10) [25 years-62 years]		39.5 (17) [25 years-77 years]
Males (n)/Females (n)	11/9		5/8
	Day 1	Day 2	
Weight [Range], kg.	83.3±13.7 [61.8-108.4]	83.5 ±13.6 [62.2-108.1]	73.4 ±16.9 [51.5-110]
Height [Range], mm.	1709± 77 [1600-1880]	1709 ± 77 [1600-1880]	1668 ± 77.5 [1560-1772]
BMI [Range], kg/m^2	28.4± 4 [22.4-40.3]	28.5± 4 [22.5-40.2]	26.3 ± 5.4 [19.2-38.9]

Intra rater reliability

The ICC coefficient of the between day scans of subcutaneous fat thickness by investigator VA was high with a ratio of 0.94 as indicated in Table 14. The Bland and Altman's plot between the differences between scans and means of scans is shown in Fig.5. The lack of relation between the differences and mean in the plot shows that there was no heteroscedasticity indicating that the measurement error was not dependent on the size of the measurement. The distribution shows that in all cases except two, the difference between scan on day 1 and scan on day 2 is less than 2 mm. The central line in the plot indicates a difference of -0.685 mm i.e., the mean of the differences. The dotted line in the plot represents two times the standard deviation of the differences (2 x 1.3) and thus indicates the limits of agreement which extend from -3.29 mm to 1.92 mm. However, there are two cases which lie outside the dotted line (two times the standard deviation of the differences).

Inter rater reliability

The inter-rater reliability of fat thickness in this study was excellent with an ICC coefficient of 0.99 (Table 15). Compared to the differences in between day scans (intra-rater reliability), the differences between scans of the two investigators were narrower with most cases having a difference less than 0.5 mm. the central line in the plot indicates the mean difference (-0.131mm) and the dotted line represent two times standard deviation of the differences between Scans VA and Scans KJ representing the limits of agreement which were between 0.9mm and – 1.0 mm (Fig. 6)

Table 14 Intra-rater reliability Means ± SD, ICC with 95% CI and agreement (LOA)

	Mean fat thickness (mm)	**Mean absolute difference (mm)**	**ICC**	**95% Confidence Interval**		**Bland Altman Limits of agreement (mm)**
				Upper Bound	**Lower Bound**	
US (Scan day1-Scan day2)	9.5±3.6 (day 1) 10.1±3.8 (day 2)	1.07	0.94	0.977	0.860	-3.3, 1.9

Table 15 Inter-rater reliability Means ± SD, ICC with 95% CI and agreement (LOA)

	Mean (mm)	**Mean absolute difference (mm)**	**ICC**	**95% Confidence Interval**		**Bland Altman Limits of agreement (mm)**
				Upper Bound	**Lower Bound**	
Scan VA	11±5.6	0.034	0.99	0.988	0.999	0.9, -1.0
Scan KJ	11.2±5.6					

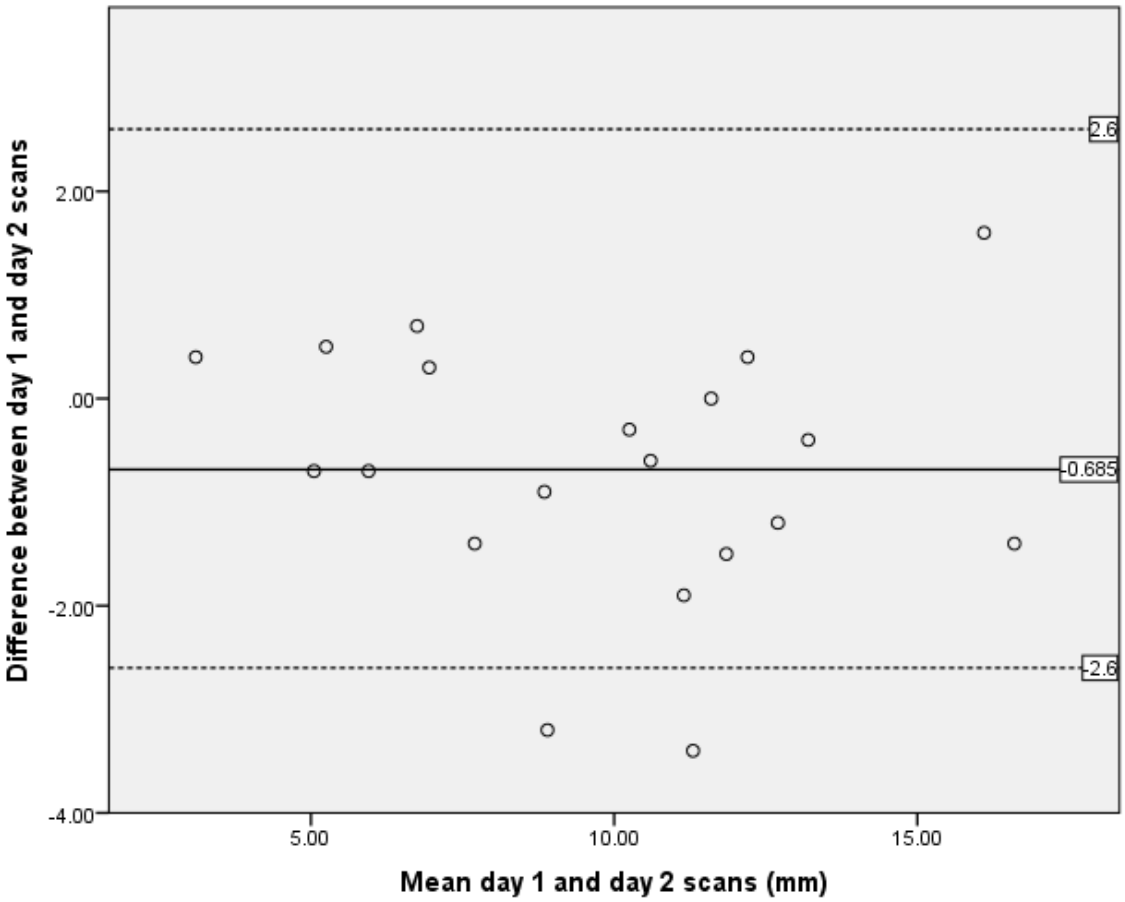

Figure 5 Bland and Altman Plot of the differences between US Scan day1 and US Scan day 2 vs. mean of US Scan day1 and US Scan day 2 for intra rater agreement

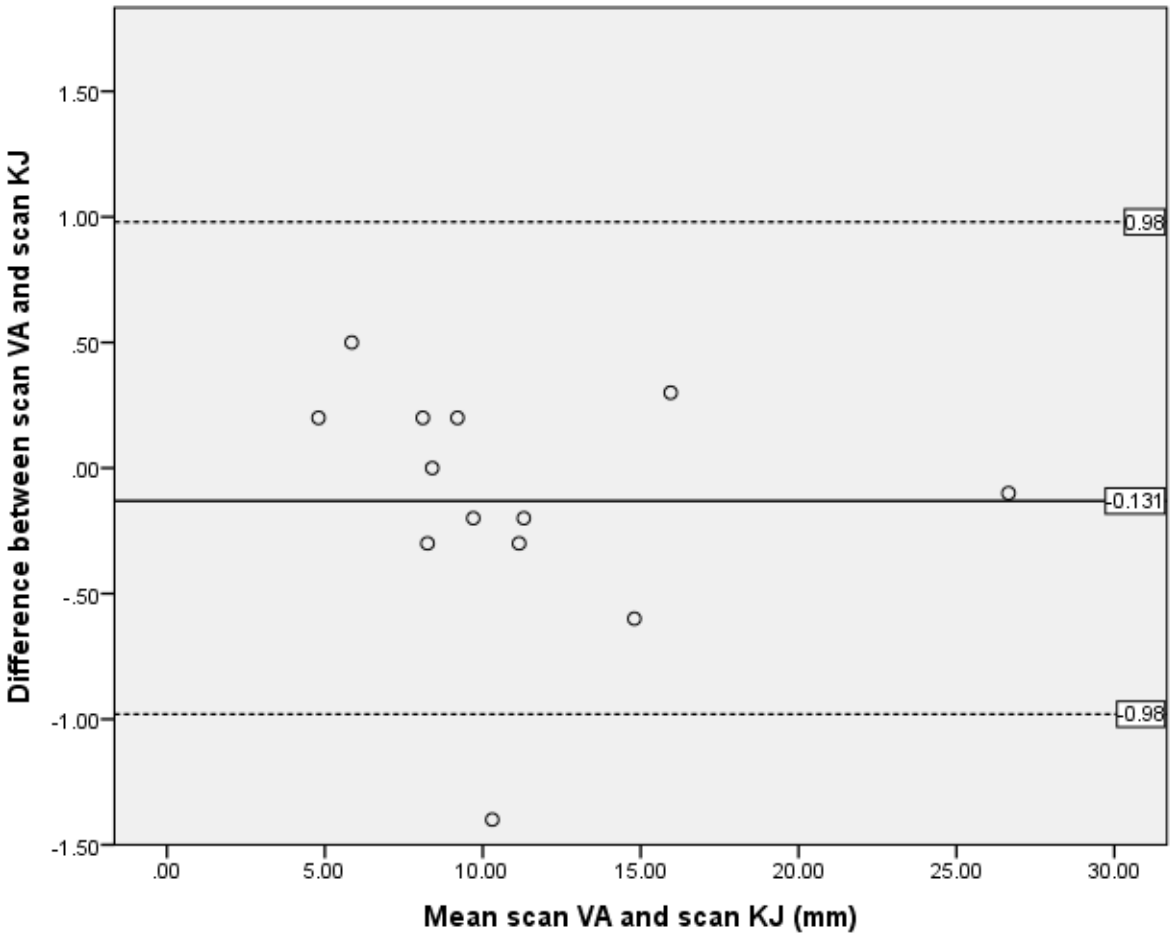

Figure 6 Bland and Altman Plot of the differences between Scan VA and Scan KJ vs. mean of Scan VA and Scan KJ for inter rater agreement.

6.7.5 Discussion

The current study aimed to assess the reliability of ultrasound measurement of subcutaneous fat thickness above the knee. A very good inter-rater (ICC = 0.99) and intra-rater (ICC = 0.94) reliability was observed for the ultrasound measurements.

The high ICC of the US measurements (0.94 for intra-rater and 0.99 for inter-rater) compares favorably to previous studies assessing intra and inter-observer reliability of US for the measurement of subcutaneous fat thickness (Ishida et al. 1992, Bellisari et al. 1993). In addition, Ishida et al. (1992) used the generalisability theory to assess the relative contribution of subjects, days, investigators and trials on the variance in the fat thickness measurements. Subjects accounted for 79-97% variation, subject by day interaction accounted for 2-12% while investigators and trials accounted for less than 1% variation. The greater variation accounted for by subject by day interaction than that due to investigator may explain the higher reliability parameters for the inter-rater test compared to the intra-rater reliability test.

However, direct comparison of our measurements to that of previous studies is not possible due to differences in the site of measurement. There are no established sites for the measurement of subcutaneous tissue using ultrasound, but some previous studies use sites for skin fold measurement given by the International Society of Kinanthropometric Assessment guidelines (Marfell Jones 2006). For the thigh area, this is at the mid-point between inguinal crease and anterior patella. The site for ultrasound measurement in this study is more distal, on anterior thigh, 7cm above the marked midpoint of the knee. The reason for the choice of this site is the proximity to the knee joint. Anthropometric measurements of the operated limb (supra patellar index) has been shown to have some effect on surgical difficulties which may subsequently have implications on surgical recovery (Lozano et al.2008). A distance of 7 cm allows accommodation for tissue folds above the knee joint particularly in obese participants.

Ultrasonography is proposed as an alternative method to skin fold measurement as it overcomes some of the limitations of skinfold measurements. Unlike skin fold

measurement, US can measure full subcutaneous fat tissue in persons with high fat mass. This was essential for the prospective study for measuring fat thickness in obese patients. In addition, ultrasound also allows screen display of adipose tissue for potentially more accurate measurements. Despite these advantages and the observed high reliability there are some limitations to the method. Firstly, constant and uniform pressure on the transducer is needed as there is a reduction of the subcutaneous fat thickness with increased force on the transducer which is suggested to have a 'squeezing out' effect on the water contained in the adipose tissue (Leahy et al. 2012). Differences in tissue thickness caused by differential pressure on the probe were also observed in this study. The second limitation is the difficulty in interpretation of images which may arise as tissue characterization is subjective and depends on experience (Bellisari and Roche 1993).Subcutaneous fat tissue is interspersed with connective tissue. Visual interpretation of the fat boundary can be affected by the connective tissue such that connective tissue near the fat-muscle interface may make the boundary between fat and muscle layer unclear (Bellisari& Roche 2005). Use of generous amount of acoustic contact gel, maximum surface contact with transducer and constant monitoring of the real time image is essential to keep the compression on the transducer to a minimum and obtain as clear an image as possible to identify the muscle fat interface.

In conclusion, the proved reliability in the current study for ultrasound imaging of subcutaneous fat thickness justifies the use of the procedure and standardization, as described in this study by the investigator, in an apparently healthy sample to obtain reliable and accurate US measurements. Furthermore, knowing the safety of the use of these body composition methods, these can be also be implemented in the prospective study on TKA patients to obtain valid measurements.

6.8. Outcome measures.

6.8.1. Oxford Knee Score

The Oxford Knee Score (OKS) is a self-report questionnaire which was specifically designed to measures the patient's perception of their knee function after total knee arthroplasty (Dawson et al. 1998). The questionnaire contains 12 questions, with five categories of response for each question. In the original scoring system for the questionnaire (as described in Chapter 5), each question is scored from 1 to 5 indicating response from least to most difficulty/severity. The individual response score is then combine to produce a final score ranging from 12 (least difficulty) to 60 (most difficulty). The current study has used the new scoring system for the questionnaire recommended by the authors (Murray et al. 1997) in which each question is scored from 0 to 4, 4 being the best outcome. This produces an overall score ranging from 0 to 48 where 48 indicate least functional difficulties. The questionnaire has been tested for validity, reproducibility and sensitivity to change (Dawson et al. 1998; Garrat et al. 1993).

For the postal questionnaires collected at six week after surgery, incomplete questionnaires were re sent to the participants after contacting them. When contact was not possible, missing data addressed as per recommendations by the authors. The questionnaire authors recommend that if only one or two questions have been unanswered, it is possible to enter the mean value representing all of their other responses in order to fill the missing data. However, if more than two questions are left unanswered, the overall score should not be calculated. If two answers were indicated for a single question, the worst response was chosen as recommended by the authors.

The questionnaire being short and simple has a high completion rate compared to other self-report knee specific questionnaire such as WOMAC or Lequesne Index of severity – Knee (Dunbar et al. 2001).

6.8.2. Short Form 12 Health Survey

Short for 12 health survey (also described in Chapter 5) is a 12 – item quality of life survey. SF 12 was derived from the Medical Outcomes Study Short Form 36 Health Survey (SF36) by the developers of SF 36 (Ware J et al. 1996). The purpose of development of the SF12 was to reduce the number of health dimensions measured by selecting 12 items from the original 36 items to produce physical component summary and mental component summary without substantial loss of information (Ware et al. 1996, Jenkinson et al. 1997).

The SF12 has been tested for validity, reliability, responsiveness by its developers and by other authors for various conditions (Ware et al., Dunbar et al. 2001, Hurst et al. 1998, Gandek et al. 1998).

SF12 has been used widely for total knee replacement patients and has shown to have a higher completed questionnaire return compared to other generic health measures SF36, Nottingham Health Profile and Sickness Impact Profile with an average time of completion of 7.7 minutes (Dunbar et al. 2001). The SF12 generates two summary score, the physical component summary (PCS) assessing the overall quality of physical health and the mental component summary assessing (MCS) overall quality of mental health. Each summary score ranges from 0 to 100, 100 indicating the best possible health.

6.8.3. Visual Analogue Scale

The Visual Analogue scale has been used extensively to assess pain in the TKA population. It has also been shown to be valid and reliable in TKA patients (Boeckstyns and Backe 1989; Flandry et al. 1991)

For the study a 100 mm scale was used on which the patient marked their level of pain. The left end of the scale indicated zero or no pain and the right end of the scale indicated 100 or maximum pain. Pain levels were assessed for pain at the knee during rest, walking, ascending stairs and descending stairs.

6.9. Data analysis

6.9.1. Data extraction

Pre-operative assessment (BMI, Waist to Hip ratio, patient characteristics) were manually recorded in the data sheet simultaneously with the assessments. These were then recorded in to SPSS data sheets. All data from the BIA was imported using the Maltron USB software for Windows and XP and Maltron data export software analyser. This data was then transferred into SPSS data sheets for analysis.

Images from the ultrasound machine were further analysed and measured on imaging software (Image J). The average of the distance between the lower surface if the skin and the top layer of quadriceps muscle was measured as the fat thickness.

Patient medical history of existing comorbidity, previous surgeries, post-operative complications and operation note were recorded manually from the patient's medical notes and entered into the data sheet.

6.9.2. Data Analysis

All data underwent descriptive analyses to describe the characteristics of the sample.

Descriptive analysis for baseline characteristics and comorbidity were done for each BMI group using number and percentages for categorical variables and mean and standard deviation for continuous variables. Between group comparison for continuous variables was done using independent t -test and categorical variables were analyzed using chi-square or Fishers exact test (if count less than five).

Complication were divided into five parts: 1) complications during hospital stay 2) complications between hospital discharge and six weeks after surgery 3) complications from six weeks to six months after surgery and 4) complications from six months to one year after surgery 5) non home bound discharge and further interventions post surgery.

Data for each complication was analyzed using counts and percentages. Chi square test and Fishers exact test (if count less than five) were employed to compare the total complication rates for each part between BMI groups.

Each body composition measure was used to divide the sample into two groups. The BMI values were divided into 2 groups of 'non-obese' (BMI = 20−29.9 kg/m^2) and 'obese' (BMI $\geq$ 30 kg/m^2), based on the WHO classification of obesity (WHO 2000). Group division of the sample for waist circumference, waist to hip ratio, body fat percentage and ultrasonography were based on a median split technique where the median value of each measure was used to divide the groups into 'low' or 'high' Correlations analysis of the body composition measures were done to assess their relationship with each other and check if they quantified obesity in the same direction.

Baseline and follow up (six weeks, six months and one year) OKS, SF12 and VAS pain scale were analyzed for time effect to assess the change from baseline to each follow up using Friedman's ANOVA and post hoc test using Wilcoxon signed rank test where appropriate.

Inferential analyses to check the null hypothesis were done in two ways:

1. Correlation analysis with Pearson's correlation coefficient and scatter plots to explore the relationship between body composition measures and OKS, SF12 and VAS pain scale.
2. ANCOVA with baseline score as covariate to assess the difference between groups for normally distributed data and Mann Whitney test to assess for group differences for data which do not meet assumptions of ANCOVA.

The level of significance was set at $p < 0.05$ for all statistical tests. All statistical analyses were carried out using SPSS version 19.0

CHAPTER 7: A PROSPECTIVE STUDY OF THE EFFECT OF BODY COMPOSITION ON TKA OUTCOMES: RESULTS AND DISCUSSION

Chapter overview

This chapter is presented in two sections. The first section (Section 8.1) reports the study assessing the effect of obesity (as defined by five body composition measurement methods) on self-report outcomes up to one year after TKA and section. The second section (Section 8.2) discusses the findings of the study and its implications

7.1. Study results

7.1.1 Section overview

This section includes reporting of participant baseline characteristics, immediate and follow up complication rates followed by descriptive data for the independent variables and outcomes. Inferential statistics are then presented addressing the hypothesis, first by assessing the relationship between obesity and outcomes using independent variables as continuous data and then by group comparison for differences between outcomes measures. This section ends with a summary of the results.

7.1.2. Baseline participant characteristics

Participant characteristics at baseline are as shown the table below (Table 16). Differences in the distribution of age and gender across the pre-operative BMI groups

were assessed using independent t- test and chi square test respectively. As shown in the table neither age nor gender distribution was significantly different across groups. Of the total patients, 6.5% (n = 4) had rheumatoid arthritis, of which more were in the non-obese group (three of four). Majority of the patients (72.13%) were fitted with a Triathlon (Stryker Ltd.) knee replacement. Other types of prosthesis included the fixed bearing, PCL retaining, Sigma PFC (DePuy Int Ltd.) (19.6%) and a Kinemax (Stryker Ltd.) fitted in one patient. The values of the count of the number of osteoarthritis/ rheumatoid arthritis, laterality, prosthesis type are also given in the Table 16.

Table 16 Characteristics of the participants at Baseline

Participant characteristic	**Total sample** **N = 61**	**Obese, BMI ≥ 30 kg/m^2** **N = 38**	**Non-obese, BMI = 25-29.99 kg/m^2** **N = 23**	**P value T-test[a]/ chi-square test[b]/fishers-exact test[c]**
Mean age in years Standard deviation	70.6 (8)	68.9 (8.4)	73.4 (6.7)	0.189[a]
Gender • Male • Female	 28 33	 17 21	 11 12	0.814[b]
Diagnosis • OA • RA	 57 4	 37 1	 20 3	0.129[c]
Laterality • Right • Left	 24 37	 16 22	 8 15	0.183[c]
Prosthesis • Triathlon • PFC • Kinemax • Not recorded	 44 12 1 4	 27 8 1 2	 17 4 0 2	

7.1.3. Comorbidities prior to surgery

Two patients with a previous episode of atrial fibrillation had been fitted with a pacemaker. One of the patients was fitted with the pacemaker after their baseline assessment for the study was completed. The other patient had a pacemaker fitted before he attended the baseline assessment for the study and in this case, since the presence of a pacemaker is a contraindication for the use of BIA, body fat percent data was not collected.

In total there were four morbidly obese patients. Participant with the highest BMI (49.1 kg/m^2) had a history of metabolic syndrome and had undergone gastric banding surgery previous to being placed on the waiting list for TKA. Three other morbidly obese patients had histories of atrial fibrillation and myocardial infarction.

The list of medical conditions obtained from patient's medical history previous to the TKA has been detailed Table 17.

Table 17 List of comorbidity previous to TKR

Medical condition	Total sample		Obese, BMI ≥ 30 kg/m^2		Non-obese, BMI = 25-29.99 kg/m^2	
	No of participants / total no of participants for which data was obtained	**% of the no of participants for which the data was obtained**	**No of participants / total no of obese participants for which data was obtained**	**% of the no of obese participants for which the data was obtained**	**No of participants / total no of non-obese participants for which data was obtained**	**% of the no of non-obese participants for which the data was obtained**
Previous pulmonary embolism	2/61	3.3%	2/38	5.3%	0	0
Cerebrovascular disease						
• TIA	1/61	1.65%	0	0	1/23	4.3%
• Stroke	4/61	6.6%	1/38	2.6%	3/23	13%
Ischemic heart disease						
• CAD	3/61	4.95%	2/38	5.3%	1/23	4.3%
• MI	6/61	9.9%	4/38	10.5%	2/23	8.7%
• AF	6/61	9.9%	3/38	7.9%	3/23	13%
• LVF	1/61	1.65%	1/38	2.6%	0	0
Hypertension	29/61	47.5%	21/38	55.3%	8/23	34.8%
Type II Diabetes*	8/61	13.1%	8/38	21%	0	0

COPD	6/61	9.9%	3/38	7.9%	3/23	13%
Breast cancer	4/61	6.6%	3/38	7.9%	1/23	4.3%
Prostrate cancer	5/61	8.25%	3/38	7.9%	2/23	8.7%
Hodgkin's disease	1/61	1.65%	0	0	1/23	4.3%
Chronic lymphocytic leukaemia	1/61	1.65%	1/38	2.6%	0	0
Metabolic syndrome	1/61	1.65%	1/38	2.6%	0	0
Fatty liver	1/61	1.65%	1/38	2.6%	0	0
Low back pain	4/61	6.6%	3/38	7.9%	1/23	4.3%
Hip pain	2/61	3.3%	2/38	5.3%	0	0
Ankle arthritis	2/61	3.3%	2/38	5.3%	0	0
Chronic ankle swelling	1/61	1.65%	1/38	2.6%	0	0
THA	4/61	6.5%	2/38	5.1%	2/23	8.7%
TKA	17/61	27.9%	10/38	25.6%	7/23	31.8%
Ankle fusion	1/61	1.65%	1/38	2.6%	0	0

*Significantly different between obese and non-obese, $p < 0.05$

Previous Knee and Hip replacements

Twenty eight percent of the total sample had undergone a previous TKA in the contralateral knee. Between the obese and non-obese groups, the non-obese group had a greater percentage with a history of a previous TKA than obese (31.8% vs. 25.6%), but this difference was not significant (two tailed p value for chi square test = 0.728)

There were two previous THR in both obese and non-obese groups. However, percentage wise, the non-obese group had a greater proportion of patients with previous THR (but not statistically significant, two tailed p value for fishers exact test = 0.628). Both patients in the obese group with THR had bilateral replacements while the two patients in non-obese group had unilateral THR.

7.1.4. Complications post surgery

The information on the reported complications obtained from patients and medical records were grouped in to those arising in the immediate post-operative period, from discharge till six weeks after surgery, from six weeks after surgery till six months after surgery and from six months after surgery till one year after surgery.

Complications during hospital stay

The details of significant complications seen during the patients' hospital stay are listed in the Table 18. There were a total of five post-operative conditions complicating the post-operative recovery. Of the six patients experiencing these complications, three were obese and two were non-obese. One patient in the obese category experienced two complications in the list, suffering from both a lower respiratory tract infection and an

onset of fast atrial fibrillation. The complications obviously increased the length of the hospital stay for the patient except in one case where a patient developed atelectasis and hypoxia but was discharged in four days once his stats were back to normal. The longest hospital stay of 15 days was recorded for the patient who developed pulmonary embolism. One patient with atrial fibrillation was discharged after six days, however, to a nursing home, for further recovery

Complications between discharge and six weeks after surgery

As shown in Table 19, of the 17 complications reported in 29 patients, 16 (42.1%) were obese and 13 (56.5%) were non-obese. One patient not listed in the table above had been readmitted because of chest pain and shortness of breath one week after discharge but on further investigation, no evidence of pulmonary embolism or any other condition was found to be reported.

Complications between six weeks and six months after surgery

Significant co-morbidities that developed in patients during this period included an episode of MI, prostate cancer, metastasis of breast cancer and duodenal ulceration (Table 20). Related directly to the operated knee, one patient developed early osteolysis and loosening under the tibial tray around six months after surgery. Further interventions for this were not immediate as the patient was undergoing aggressive chemotherapy and also antibiotic therapy for urinary tract infection post prostrate biopsy and therefore information regarding further interventions in this case was not present in the medical notes. Of a total of 13 participants with a complication during this period, 9 (23.7%) were observed on the obese and 4 (17.4%) were observed in the non-obese.

Complications between six months post operation and one year after surgery

Details of the co-morbidities/ complications developed during this period are listed in the table below (Table 21). One patient was deceased after a period of palliative care for multiple brain metastasis of her breast cancer. During this period, five (13.1%) obese and two (8.7%) non-obese had a complication.

Non- home bound discharge and further interventions after surgery

Details of non- home bound discharge, interventions and referrals are shown in the Table 22. A patient aged 89 was discharged into a geriatric orthopaedic rehabilitation after discharge from the hospital. A patient was discharge to a rehabilitation ward while another patient who developed atrial fibrillation post-operatively was discharged to a nursing home for convalescence. Five patients were referred by the hospital or the arthroplasty practitioners to outpatient or domiciliary physiotherapy. Some patients may have accessed physiotherapy through self-referral, the information for which, however, we could not extract from the patient notes. One patient was referred to psychology and was under anti-depressant medication for depression related to bereavement in the family and social circumstances. This also hindered her motivation for recovery in the early post-operative stages.

Post-operative complications: Summary of results

The number of co-morbidities or complications developed after surgery decreased over the period from discharge to one year after surgery from 28 in the period between discharge and six weeks to six for that between six months and one year after surgery. Related to the knee, complications documented varied from superficial wound infection, wound leakage, wound inflammation and continued pain, stiffness and muscle spasm

around the operated knee. In two cases, continued knee pain and stiffness was reported even in the later stages of recovery between six months and one year. Increased pain in the contralateral knee was experienced in four cases, of which three were reported before six months and one was reported after six months after surgery.

Major complications such as deep infection, prosthetic infection or prosthetic fractures were not documented for any case and neither was any requirement for a revision surgery in any case noted. As mentioned in previous section, there was a case with early osteolysis under the tibial tray for one patient although information on further interventions for this was not available.

Table 18 List of complications during hospital stay

Complications during hospital stay (immediate post-operative recovery)	Total sample		Obese, BMI ≥ 30 kg/m^2		Non-obese, BMI = 25-29.99 kg/m^2	
	No of participants / total no of participants for which data was obtained	% of the no of participants for which the data was obtained	No of participants / total no of obese participants for which data was obtained	% of the no of obese participants for which the data was obtained	No of participants / total no of non-obese participants for which data was obtained	% of the no of non-obese participants for which the data was obtained
Atelectasis	1/61	1.6%	0	0	1/23	4.3%
Pulmonary embolism	1/61	1.6%	1/38	2.6%	0	0
Respiratory infection	1/61	1.6%	1/38	2.6%	0	0
Atrial fibrillation	2/61	3.3%	1/38	2.6%	1/23	4.3%
Anxiety and stress	1/61	1.6%	1/38	2.6%	0	0
Total number of complications*	6/61	9.8%	4/38	7.9%	2/23	8.7%

*Two tailed p-value for fishers exact test= 1

Table 19 List of complications from hospital discharge till 6 weeks post operation

Complications (discharge to 6 weeks post op)	Total sample		Obese, BMI ≥ 30 kg/m^2		Non-obese, BMI = 25-29.99 kg/m^2	
	No of participants / total no of participants for which data was obtained	% of the no of participants for which the data was obtained	No of participants / total no of obese participants for which data was obtained	% of the no of obese participants for which the data was obtained	No of participants / total no of non-obese participants for which data was obtained	% of the no of non-obese participants for which the data was obtained
DVT	1/61	1.6%	0	0	1/23	4.3%
Lower respiratory tract infection	1/61	1.6%	0	0	1/23	4.3%
Wound infection	2/61	3.3%	1/38	2.6%	1/23	4.3%
Wound leakage	2/61	3.3%	1/38	2.6%	1/23	4.3%
Cellulitis	1/61	1.6%	0	0	1/23	4.3%
Wound inflammation	1/61	1.6%	0	0	1/23	4.3%
Stiffness	4/61	6.5%	2/38	5.3%	2/23	8.7%
Abdominal discomfort due to analgesia	4/61	6.5%	2/38	5.3%	2/23	8.7%
GI bleed due to analgesia	2/61	3.3%	2/38	5.3%	0	0
Ulceration due to analgesia	2/61	3.3%	2/38	5.3%	0	0

Contralateral knee pain	2/61	3.3%	2/38	5.3%	0	0
Hip pain	1/61	1.6%	1/38	2.6%	0	0
Foot pain	2/61	3.3%	0	0	2/23	8.7%
Sciatica pain	1/61	1.6%	1/38	2.6%	0	0
Depression	1/61	1.6%	1/38	2.6%	0	0
Panic attacks	1/61	1.6%	1/38	2.6%	0	0
Maculopapular rash	1/61	1.6%	0	0	1/23	4.3%
Total number of complications[*] 17	29/61	47.5%	16/38	42.1%	13/23	56.5%

[*]Two tailed p-value for Chi square test = 0.275

Table 20 List of complications from 6 weeks to 6 months post operation

Complications (6 weeks post op to 6 months post op)	Total sample		Obese, BMI ≥ 30 kg/m^2		Non-obese, BMI = 25-29.99 kg/m^2	
	No of participants / total no of participants for which data was obtained	% of the no of participants for which the data was obtained	No of participants / total no of obese participants for which data was obtained	% of the no of obese participants for which the data was obtained	No of participants / total no of non-obese participants for which data was obtained	% of the no of non-obese participants for which the data was obtained
MI	1/61	1.6%	1/38	2.6%	0	0
Metastasis of breast cancer	1/61	1.6%	1/38	2.6%	0	0
Duodenal ulcer and gastritis	1/61	1.6%	1/38	2.6%	0	0
Prostrate cancer	1/61	1.6%	0	0	1/23	4.3%
Decreased balance	1/61	1.6%	1/38	2.6%	0	0
Early osteolysis of tibial tray	1/61	1.6%	0	0	1/23	4.3%
Knee stiffness	1/61	1.6%	0	0	1/23	4.3%
Continued knee pain + calf pain	1/61	1.6%	0	0	1/23	4.3%
Continued knee pain and muscle spasm	1/61	1.6%	1/38	2.6%	0	0
Contralateral knee pain +arthritis	2/61	3.3%	2/38	5.3%	0	0

Continued knee pain and redness	1/61	1.6%	1/38	2.6%	0	0
Soft tissue knee injury due to fall	1/61	1.6%	1/38	2.6%	0	0
Total number of complications* 12	13/61	21.3%	9/38	23.7%	4/23	17.4%

*Two tailed p-value for fishers exact test = 0.749

Table 21 List of complications from 6 months till 1 year post operation

Complications (6 months post op to one year post op)	Total sample N = 61		Obese, BMI ≥ 30 kg/m^2 N = 38		Non-obese, BMI = 25-29.99 kg/m^2 N = 23	
	No of participants / total no of participants for which data was obtained	% of the no of participants for which the data was obtained	No of participants / total no of obese participants for which data was obtained	% of the no of obese participants for which the data was obtained	No of participants / total no of non-obese participants for which data was obtained	% of the no of non-obese participants for which the data was obtained
MI	1/61	1.6%	1/38	2.6%	0	0
Subdural haematoma (recovered with IC surgery)	1/61	1.6%	0	0	1/23	4.3%
Stroke	1/61	1.6%	1/38	2.6%	0	0
Continued pain and stiffness	2/61	3.3%	1/38	2.6%	1/23	4.3%
Contralateral knee pain	1/61	1.6%	1/38	2.6%	0	0
Total number of complications[*] 6	7/61	11.5%	5/38	13.1%	2/23	8.7%

*[*]Two tailed p-value for fishers exact test = 0.700

Table 22 List of non home bound discharges, further interventions and referrals

Intervention	Total sample		Obese, BMI ≥ 30 kg/m^2		Non-obese, BMI = 25-29.99 kg/m^2	
	No of participants / total no of participants for which data was obtained	% of the no of participants for which the data was obtained	No of participants / total no of obese participants for which data was obtained	% of the no of obese participants for which the data was obtained	No of participants / total no of non-obese participants for which data was obtained	% of the no of non-obese participants for which the data was obtained
Discharge to rehab/nursing home	3/61	4.9%	1/38	2.6%	2/23	8.7%
Discharge to observation ward (for mild cellulitis)	1/61	1.6%	0	0	1/23	4.3%
Contralateral TKR	1/61	1.6%	0	0	1/23	4.3%
Revision contralateral TKR	1/61	1.6%	1/38	2.6%	0	0
Revision THR	1/61	1.6%	1/38	2.6%	0	0
Referrals						
Out patient physiotherapy	5/61	8.2%	2/38	5.3%	3/23	13%
Orthotics for foot pain	1/61	1.6%	0	0	1/23	4.3%
Psychologist	1/61	1.6%	1/38	2.6%	0	0

7.1.5. Measurement of body composition

The average BMI of the total sample was 31.3 kg/m^2 with a wide variation in the BMI values which ranged from 20.7 to 49.1 kg/m^2 (Table 23). When grouped according to the established cut-offs for BMI (WHO 2000), a larger proportion of the sample were obese (62.3%). The average BMI for the non-obese group was 26.2 kg/m^2 while for the obese group it was 34.4 kg/m^2. There were four morbidly obese patients in the total sample with BMI ranging from 40.3 to 49.1 kg/m^2. For statistical analysis, however, due to a low number the morbidly obese were grouped in the obese category.

Waist circumferences were first grouped into low risk ($\leq$ 40 inches for males and $\leq$ 35 inches for females) and high risk (> 40 inches for males and >35 inches for females) and Waist to hip ratio measurements were grouped into values of WHR >0.90 (males) WHR>0.85 (females). This classification was based on the WHO cut-off values for WC and WHR for classifying those with abdominal obesity (WHO 2008). A large majority of the sample (86%) fell into the 'high risk' or 'abdominal obesity' group while only 14 % were in the 'low risk' or 'no abdominal obesity' group. Similarly, there was marked disparity in the number of participants in the two groups for body fat percentage (BF %) when classed as obese (BF % > 42% for females and >30% for males) and non-obese (BF % $\leq$ 42% for females and $\leq$ 30% for males) (Gallagher et al. 2000) with a greater proportion of the sample (70.5%) classed as obese. Since the large variation between group sizes (WC: 14 vs. 47, WHR: 9 vs. 52, BF%: 13 vs. 43) would render the statistical analysis meaningless, these body composition measures were split into two groups using a median split technique. Since no established or proposed cut-off points to classify obesity by ultrasound measurement of fat thickness are known, the median was calculated for the ultrasound measurements as 11.167 mm and the fat thickness value of 11.167 mm was used to split the sample into two groups as was done for WC, WHR and BF% groups.

Descriptive values of the baseline body composition groups are detailed in table 23

Table 23 Body Composition groups

BMI groups using WHO classification		**Non-obese<30 kg/m^2**	**Obese ≥ 30 kg/m^2**
	N	23 (37.7%)	38 (62.3%)
	Mean weight (kg), (SD)	73.2(12.1)	92.5(17.7)
	Mean height (mm), (SD)	1666 (96)	1636(94)
	Mean BMI (kg/m^2), (SD)	26.24 (2.7)	34.36 (4.4)
WC (mm) median split groups		**WC <1054 (41.5")**	**WC ≥1054 (41.5")**
	N	31	30
	Mean WC (SD)	37.3 (3.3)	45.9 (3.5)
WHR median split groups		**WHR < 0.95**	**WHR ≥ 0.95**
	N	32	29
	Mean WC (SD)	38.9 (5.5)	44.4 (3.8)
	Mean HC (SD)	43 (4.7)	43.5 (3)
	Mean WHR (SD)	0.9 (0.05)	1 (0.04)
BF% median split groups		**BF % < 39.9**	**BF% ≥ 39.9**
	N	30	30
	Mean fat % (SD)	33.8 (4.8)	48.2 (5.6)
US (mm) median split groups		**Fat thickness < 11.167mm**	**Fat thickness ≥11.167mm**
	N	30	31
	Mean fat thickness (SD)	7.6 (2)	15 (4)

BMI (Body Mass Index), WC (Waist Circumference), WHR (Waist to Hip Ratio), BF(Body Fat), US (Ultrasonography)

Correlations between body composition measures

Correlation analysis was performed between the body composition measures to assess the relationships between these measures and to check if they all quantify obesity in a similar direction (Table 24). All of the five body composition measures showed a significant correlation with at least two of the other four measures. Correlation coefficient (r) values ranged from 0.319 to 0.866. Only WHR and BF% ($r = -0.105$, $p = 0.424$) and WHR and ultrasound ($r = -0.118$, $p = 0.364$) did not correlate significantly. The lack of relation between WHR and BF% and US values indicate the different aspects of obesity measured by these methods. While BIA and US methods measure the actual fat present in the body (BIA) and above knee region (US), WHR gives the ratio of fat distribution i.e., greater WHR giving indication of greater central or trunk mass. Therefore greater central mass (android obesity) may be indicated by a greater WHR and body fat percentage (BIA), but in patients with more equitable distribution of body fat at both waist and hip would or those with greater fat mass at hip (gynoid obesity) will have a lower WHR but a high body fat percentage and regional fat thickness

Table 24 Pearson's Correlation between body composition measures

		BMI	WHR	WC	BF%	US
BMI	Pearson Correlation	1	.415**	.866**	.596**	.510**
	P value		.001	.000	.000	.000
	N	61	61	61	60	61
WHR	Pearson Correlation	.415**	1	.740**	-.105	-.118
	P value	.001		.000	.424	.364
	N	61	61	61	60	61
WC	Pearson Correlation	.866**	.740**	1	.373**	.319*
	P value	.000	.000		.003	.012
	N	61	61	61	60	61
BF%	Pearson Correlation	.596**	-.105	.373**	1	.619**
	P value	.000	.424	.003		.000
	N	60	60	60	60	60
US	Pearson Correlation	.510**	-.118	.319*	.619**	1
	P value	.000	.364	.012	.000	
	N	61	61	61	60	61

7.1.6. Outcomes measurement

Flow of participants in the study

The flow of participants through the study is as shown in figure 7. Twenty four (25%) of the total respondents could not be assessed for the study. Of these ten were not assessed because they were removed from the TKA waiting list or deferred from surgery, either due to development of other medical conditions requiring more immediate attention or by patients own choice of not going ahead with the surgery. Knee arthroplasty patients are given a choice of being transferred to other hospitals as a part of the waiting times initiative by the NHS Scotland to reduce the waiting time between referral and treatment. Four respondent patients were transferred to the Golden Jubilee National Hospital and one was transferred to a private hospital in Murrayfield as a part of this initiative and hence could not be assessed at their pre admission appointment for the study. Further seven participants had their pre admission clinic appointment in 2011and therefore could not be assessed. Two potential participants changed their minds about participation in the study at the pre admission clinic.

With 70 remaining respondents, the study had a dropout rate of 14% (n = 9). From the nine patients who dropped out of the study, six had their TKA surgery cancelled at or after the pre admission clinic appointment (due to cardiac condition, development of malignant bladder cancer and patient's decision of not going ahead with the surgery). Three did not respond to the six week follow up questionnaires leaving 61 complete data sets at six weeks follow up. The six month and one year follow up was obtained from the hospital database and was available for 45 (six month OKS follow up), 32 (six month SF-12 follow up) and 32 (one year OKS and SF-12 follow up).

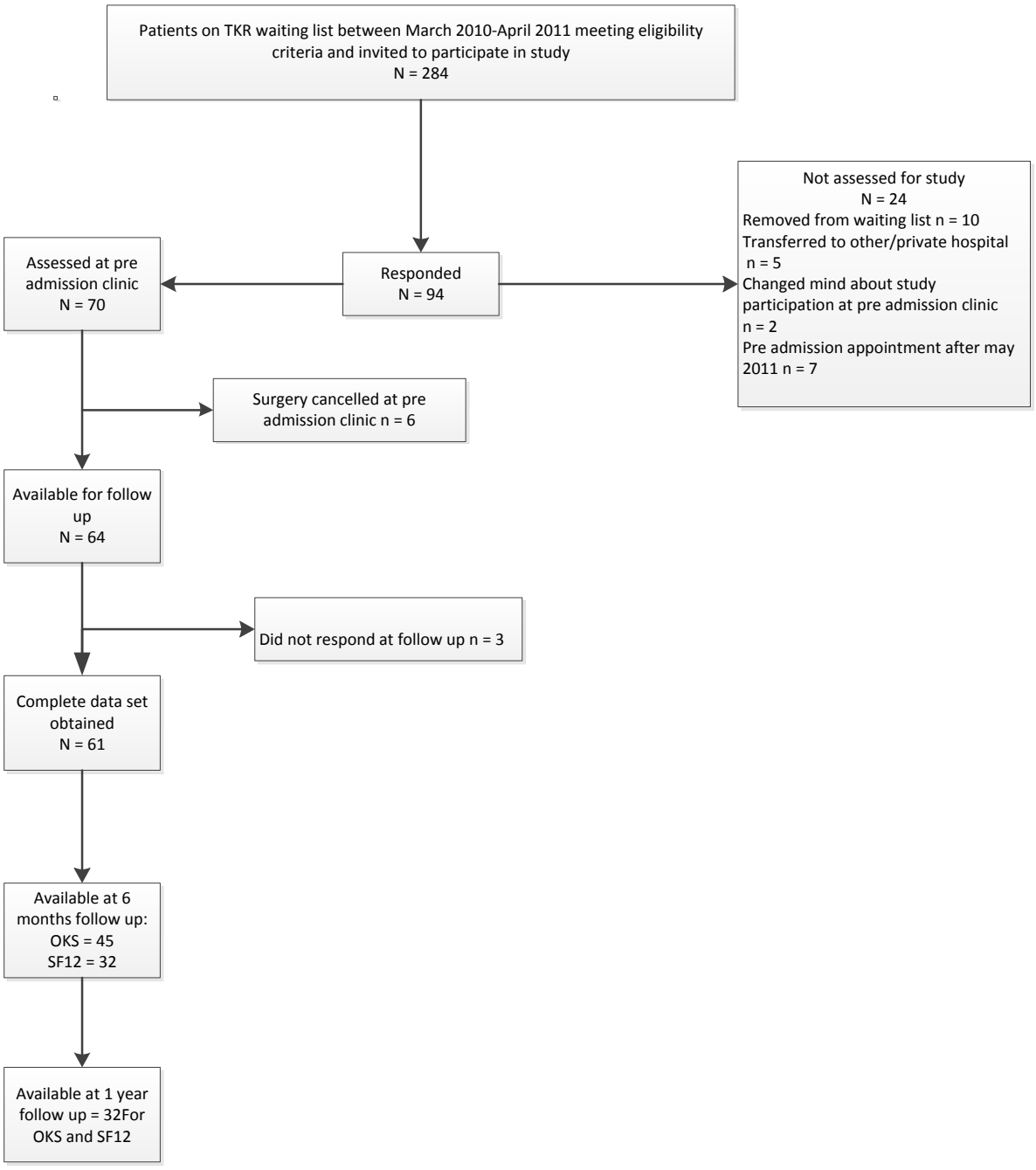

Figure 7 Flow of participants in the study

Normality tests

VAS pain scale scores and MCS of the SF12 were significantly deviated from a normal distribution. Six month and one year OKS and PCS of SF12 also showed significant deviation from normality. Baseline and six weeks OKS and PCS of SF12 were normally distributed. All tests for normality have been shown in the Appendix B.

Baseline primary outcomes measure

Oxford Knee Score

The Oxford Knee Score (OKS) calculated between 0 and 48 (48 as the best outcome) had a median score of 22 (IQR = 9). A wide variation was seen with scores as high as 36 to scores as low as nine. However, on removing the extreme values, the 5 % trimmed mean was 21 and close to the mean of the sample indicating little influence of outliers on the sample mean. The descriptive statistics for the pre operative OKS are shown in Table 25.

Baseline secondary outcomes measure

Short Form – 12 Health survey

The average physical component score, PCS, in the sample was lower than the mental component score, MCS (31.3 vs. 51.46). Out of a score of 0 to 100 (100 indicating the highest level of health, the median value was 29.8 (IQR = 9.9) for PCS. Median score for the MCS was 55 (IQR = 20.7) indicating some difference in the mean and median for MCS. The descriptive statistics for the SF12 scores are as shown in Table 25.

VAS Pain scale

The baseline scores for the pain scales were available for 59 participants of the total 61, and 55 of 61 for pain scale on stair descending. The highest average pain score was observed during stair descending (7.4± 2.21) followed by stair climbing (6.97± 2.15), walking (6.92± 1.83) and then at rest (3.5± 2.26). Larger standard deviations for pain scale values during stair mobility might indicate differences in the use of support, climbing or descending patterns used and larger standard deviation for pain at rest might indicate difference in the pattern of pain though the day/night. The descriptive statistics for pain scales are as indicated in Table 25.

Follow up primary outcomes measure

Oxford Knee Score

Six weeks scores were obtained for all participants, but the six months and one year OKS were available for 45 and 32 participants respectively. Maximum score of 48 (which is the highest possible score on OKS) was also achieved by patients as early as six weeks post-operatively. The six weeks post-operative scores did not show a significant deviation from normal distribution. Multiple modes and a high degree of deviation to the right were observed for the six month score with 42% of the six month scores above 40. The one year score were also skewed to the right and 18.8% of the total one year scores were the highest score of 48. There was a decrease in sample size in the subsequent follow up periods (N = 61 at 6 weeks, 45 at 6months and 32 at one year follow up).
Table 25 gives the means, standard deviations and participant numbers for the follow up scores. A steady increase in the mean score was observed from baseline to one year follow up (21.13, 30.86, 36.33 and 39.96). On performing a Friedman's ANOVA, significant improvement was observed from pre operative to six weeks and from six weeks to six months, ($p < 0.001$). However, the change from six months to one year follow up was not statistically significant ($p= 0.05$) as indicated in Table 25.

Follow up secondary outcomes measure

Short Form 12 (SF12)

Means, standard deviations and number of participants for all outcome measures are given in table 25. On observing the means, an increasing trend is seen for both PCS and MCS indicating a shift to better quality of life from baseline to six weeks and six month follow up. However, on performing Friedman's ANOVA (followed by post hoc test with Wilcoxon signed-rank test), it was observed that the MCS scores did not differ significantly across time points. There was a significant increase in the PCS score across the time points from baseline to one year ($p < 0.001$), although this increase is not seen between six months and one year follow up ($p = 0.85$). As with OKS, the sample size for SF12 reduced at subsequent follow ups, from 60 at six weeks to 48 and 32 for six months and one year follow up respectively.

VAS Pain scale

All pain scale values (at rest, walking stair ascending and stair descending) showed a significant reduction from baseline to six weeks indicating reduction in pain during these activities from the baseline to six weeks after the operation (Wilcoxon signed rank test, all $p < 0.001$). Pain scores were collected only at baseline and six weeks post-operative time point.

Table 25 Mean/median, standard deviation/range and N values for all outcomes measures at baseline, 6 weeks, 6 months and 1 year follow up (time effect)

Outcome measure		Baseline	6 weeks	6 months	1 year
OKS	Mean (sd)	21.13 (6.23)	30.86 (9.32) *	36.33 (9.81)*	39.96 (7)
	N	61	61	45	32
PCS	Mean (sd)	31.29 (7.34)	37.68 (9.68) *	45.34 (15.5) *	45.33 (9.33
	N	61	60	48	32
MCS	Median (IQ)	55 (20.7)	55.6 (15.65)	57.68 (9.78)	58.33 (9.37)
	N	61	60	48	32
Pain rest	Median (IQ)	3.2 (3.4)	1.3 (2.6) *	NA	NA
	N	59	59	NA	NA
Pain walking	Median (IQ)	7.5 (2.6)	2 (3.1)*	NA	NA
	N	59	59	NA	NA
Pain stair ascend	Median (IQ)	7.5 (3)	1.9 (3.8)*	NA	NA
	N	59	59	NA	NA
Pain stair descend	Median (IQ)	8 (2.8)	2.2 (5.18)*	NA	NA
	N	55	58	NA	NA

*Significant at $p < 0.05$ from baseline to six weeks and six weeks to six months

7.1.7. Effect of body composition on outcomes: Testing of hypothesis

Null hypothesis*:* Obesity (body composition) does not have any effect on self-report outcomes (OKS, SF12 and Pain scores) following TKA.

The hypothesis was tested in two ways. Firstly, correlation analysis and scatter plots were employed to explore the relationship between the body composition measures and the TKA outcomes (Section 7.1.8). Secondly, the sample was grouped according to each body composition measure followed by use of appropriate statistical method for group comparison (Section 7.1.9). Fig 9 below illustrates the different statistical methods used to address the hypothesis.

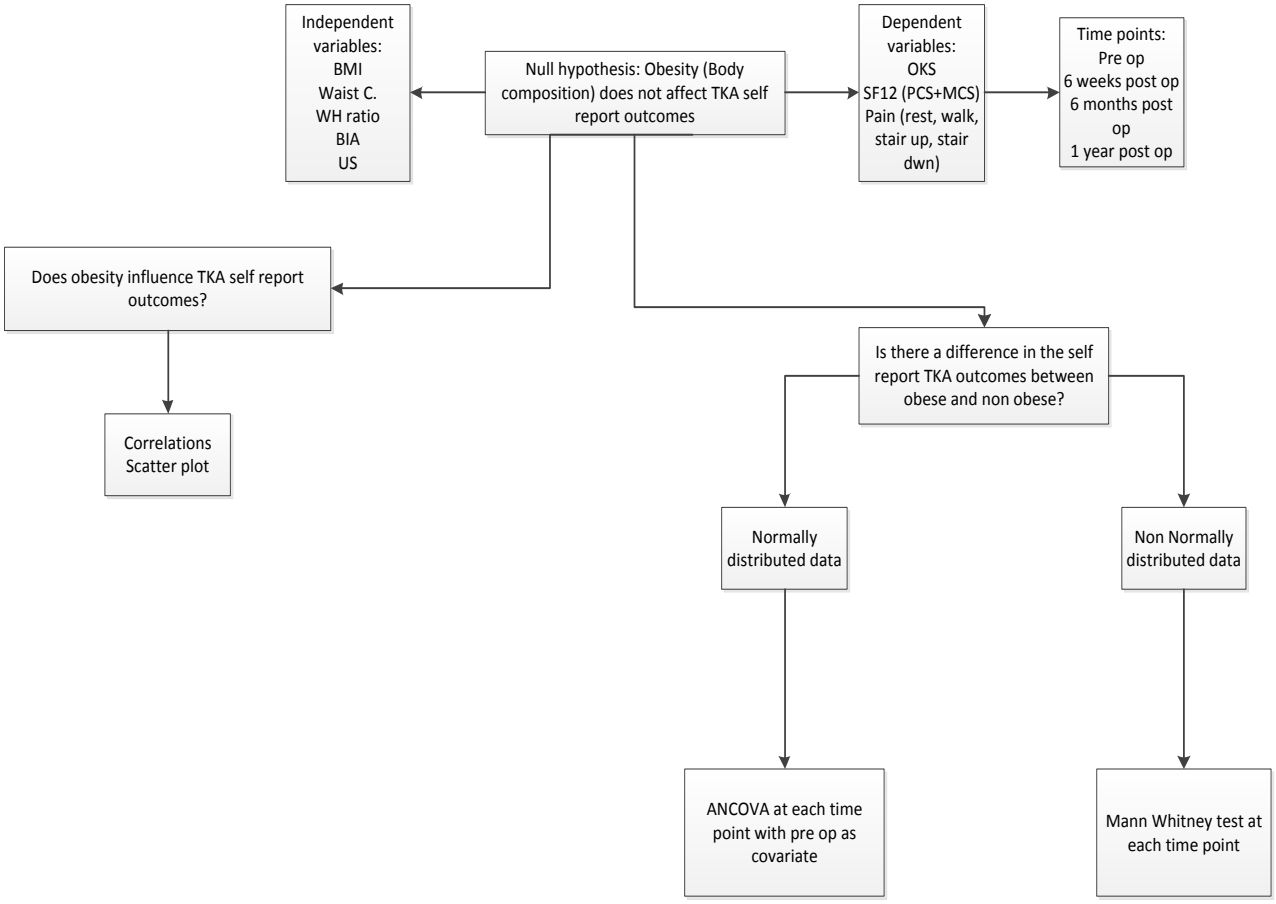

Figure8 Statistical analyses of data

7.1.8. Effect of body composition: Correlation

Correlation analysis statistics for all follow up outcomes has been given in table 26.

Body composition and OKS

Correlation analysis between the body composition measures and outcomes indicated a significant negative relationship between BMI and follow up scores at six months ($r = -.34$, $p = .024$) and one year ($r = -.42$, $p = .018$). Also a significant negative relationship was seen between waist circumference and OKS follow up scores at 6 months ($r = -.33$, $p = .027$) and one year ($r = -.38$, $p = .033$). These values therefore indicated that as BMI or waist circumference values increased, there was a decrease in score (poorer outcome). Waist to hip ratio, body fat percent and ultrasound fat thickness measures did not relate significantly to these follow up scores. None of the correlations between six week scores and any body composition measure were significant either. Correlation coefficients, p values and number of participants have been given in table 26 with significant correlations highlighted.

Scatter plots are shown for significant correlations in Figures 10-16. The negative correlation can be seen in the scatter plot for BMI vs. OKS at six months ($r^2 = .11$) (Fig. 10). The majority scores appear to be between BMI of 25 and 35 kg/m^2. In this BMI range (25 to 35 kg/m^2), the negative association does not appear strong with scores widely spread out in this region. However, the lowest OKS score of 10 is seen in two cases and these lie between BMI of 30 and 35.

Figure 11 shows the scatter plot for BMI vs. OKS one year ($r^2 = .17$). Like for BMI and OKS at six months, most scores are between BMI range of 25 and 35 kg/m^2 and appear to be largely spread out. Only two scores were below an OKS score of 30, while one was close to 30 at 29 (BMI = 33), another was an extremely low value of 21 (BMI = 49).

Scatter plots for WC vs. OKS at six months and one year are shown in Fig. 8.5. Again the majority of the scores for both outcomes lie between waist circumference of 35 to 45 inches and as seen with BMI, the values are quite spread. For OKS at six months, two cases with WC greater than 40 inches had extremely low OKS value of 10. All values of OKS at 1 year were above 30 except one value of 29 (WC = 44.5 inches) and one extremely low value of 21 (WC = 52 inches).

Body composition and SF12

Correlation analysis between body composition measures and PCS scores revealed a significant negative relationship between BMI and PCS at one year ($r = -.37$, $p = .04$) and waist circumference and PCS at six months ($r = -.29$, $p = .04$). Scatter plots for the significant relationships have been shown in Fig. 8.3 -8.8. Majority of the PCS scores were between 30 and 60. An extreme low PCS score of 23.42 (BMI = 49) was seen in the scatter plot between BMI and PCS at one year. The scatter plot between waist circumference and PCS at six months shows two extremely high PCS scores of 99 (WC = 38, 36). No significant relation was observed for any other body composition measure and PCS score.

No significant relation was observed for any body composition measure and MCS scores at any time point, except for WHR which showed a significant negative relationship with MCS at six months ($r = -.32$, $p = .03$). Here again, the scatter plot shows two extremely high MCS scores of 99 with WHR <0.90

Body composition and Pain scores

No significant relations were observed for the follow up pain scores with any of the body composition measures.

Table 26 Pearson's correlation analysis between body composition measures and all outcomes

Outcome		BMI	WC	WHR	BF%	US
OKS 6 weeks	R	-.141	-.107	-.075	.132	-.086
	Sig	.278	.414	.564	.315	.512
	N	61	61	61	60	61
OKS 6 months	R	**-.337***	**-.330***	-.202	.084	-.143
	Sig	.024	.027	.183	.587	.350
	N	45	45	45	44	45
OKS 1 year	R	**-.416***	**-.378***	-.116	-.147	-.287
	Sig	.018	.033	.528	.423	.111
	N	32	32	32	32	32
PCS 6 weeks	R	-.145	-.220	-.188	.077	-.161
	Sig	.268	.091	.150	.563	.218
	N	60	60	60	59	60
PCS 6 months	R	-.203	**-.292***	-.264	.049	-.099
	Sig	.167	.044	.070	.744	.503
	N	48	48	48	47	48
PCS 1 year	R	**-.365**	-.325	-.114	-.086	-.265
	Sig	.040	.070	.534	.640	.142
	N	32	32	32	32	32
MCS 6 weeks	R	-.089	-.028	-.067	.110	-.122
	Sig	.496	.829	.610	.402	.348
	N	61	61	61	60	61

MCS 6 months	R	-.016	.073	**-.319***	.173	-.061
	Sig	.903	.581	.027	.191	.641
	N	48	48	48	48	48
MCS 1 year	R	-.158	-.253	.070	.101	-.011
	Sig	.283	.083	.703	.499	.940
	N	32	32	32	32	32
Pain at rest 6 weeks	R	.034	.026	.133	-.147	.126
	Sig	.797	.846	.316	.272	.340
	N	59	59	59	58	59
Pain walking 6 weeks	R	.187	.176	.147	-.034	.080
	Sig	.156	.182	.266	.801	.549
	N	59	59	59	58	59
Pain stair climb 6 weeks	R	.185	.240	.255	-.161	-.023
	Sig	.161	.067	.051	.226	.864
	N	59	59	59	58	59
Pain stair descend 6 weeks	R	.169	.191	.124	-.078	.073
	Sig	.206	.152	.352	.567	.584
	N	58	58	58	57	58

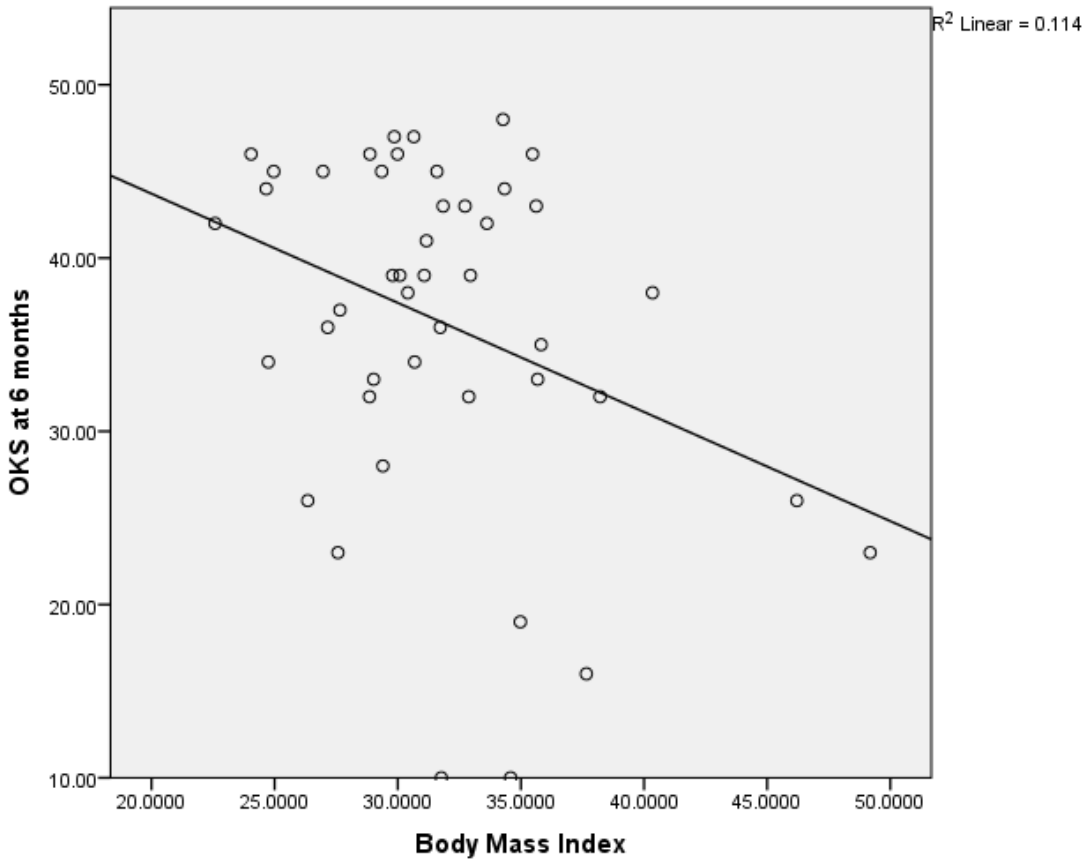

Figure 9 Scatter plot showing relationship between BMI (kg/m2) and OKS at six months follow up

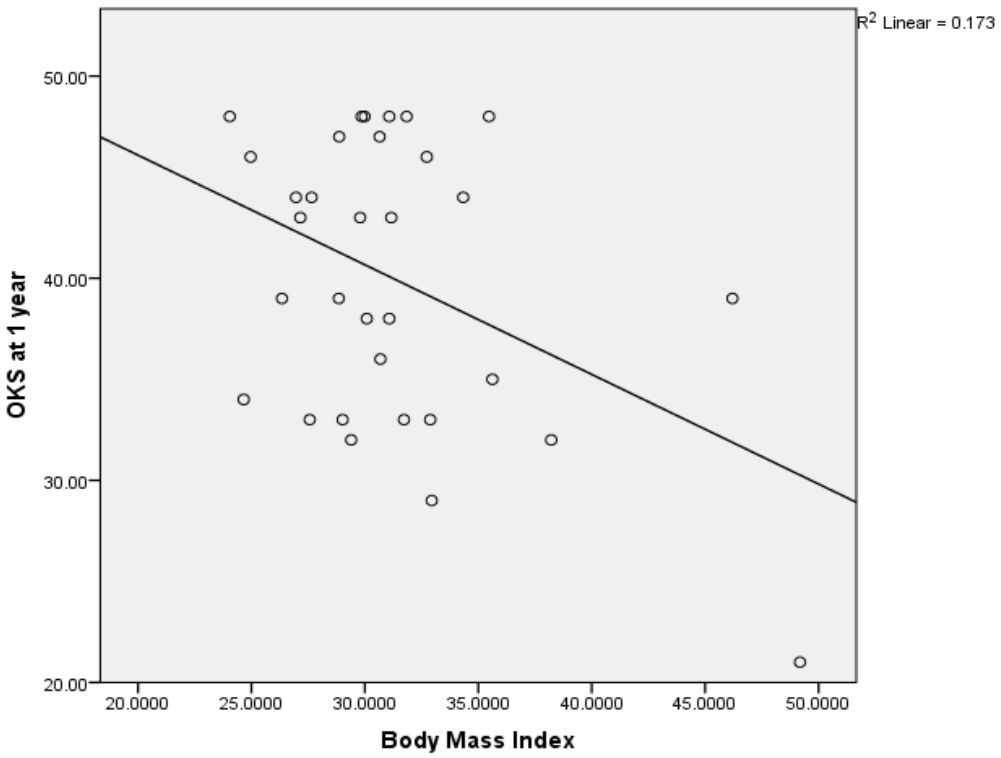

Figure 10 Scatter plot showing relationship between BMI (kg/m2) and OKS at one year follow up

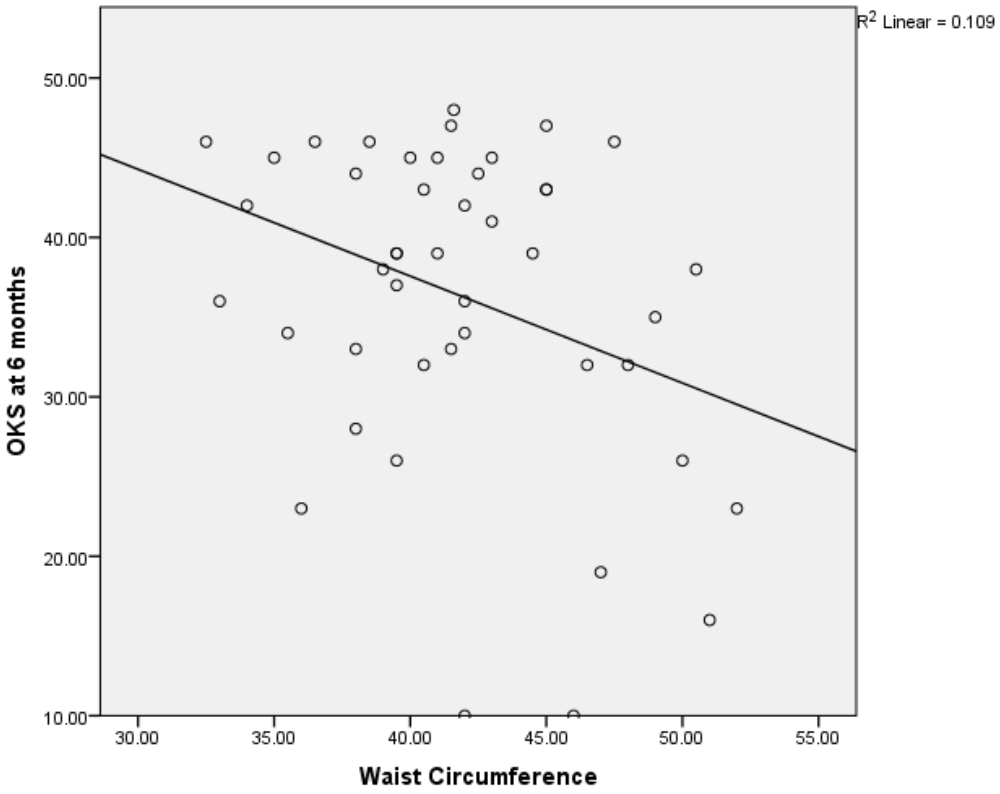

Figure 11 Scatter plot showing relationship between WC (inches) and OKS at six months follow up

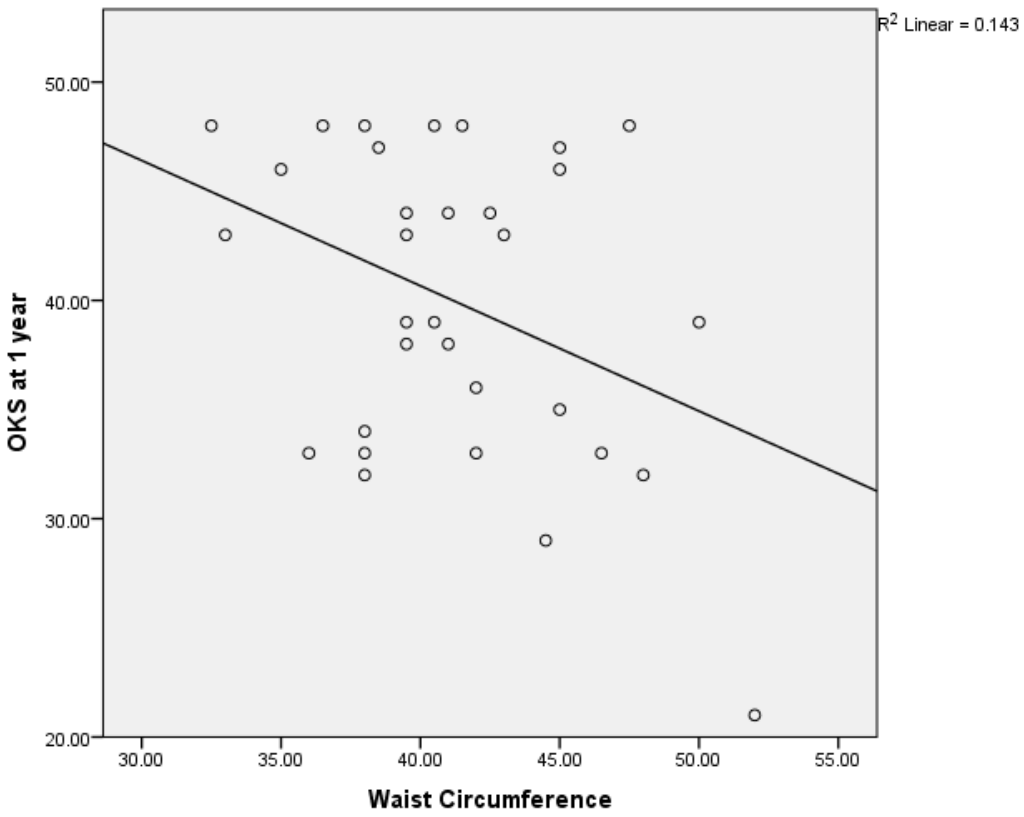

Figure 12 Scatter plot showing relationship between WC (inches) and OKS at one year follow up

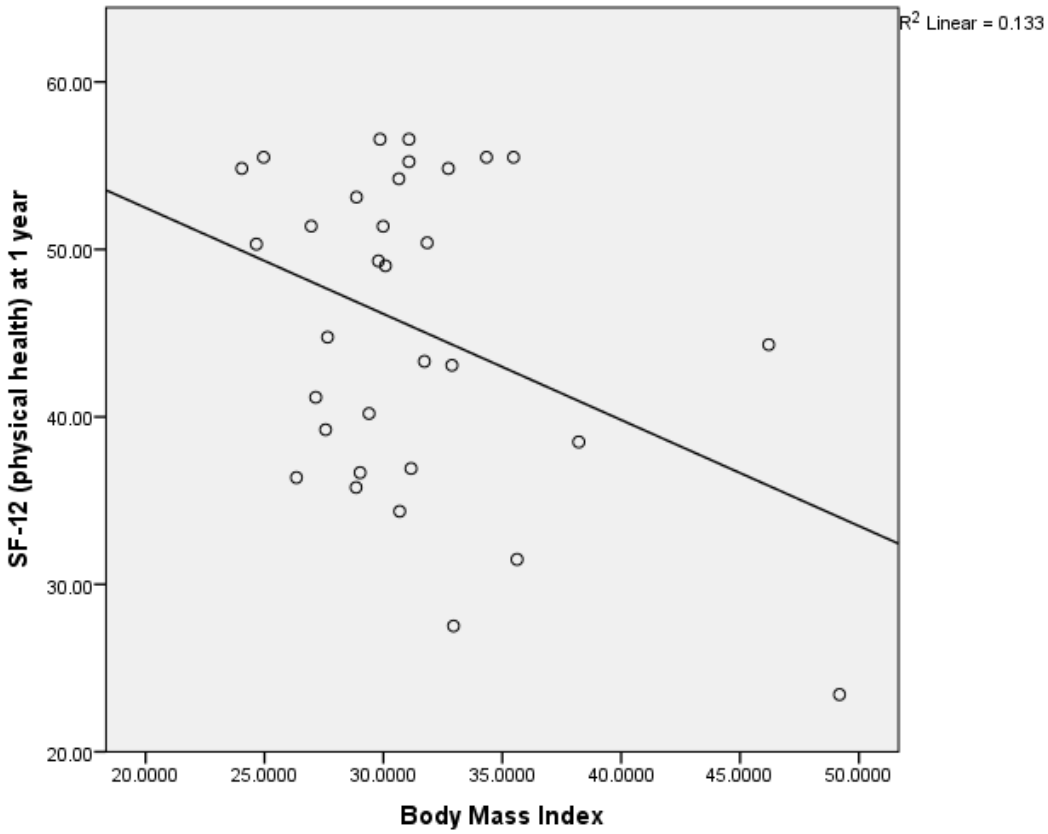

Figure 13 Scatter plot showing relationship between BMI (kg/m2) and PCS of SF-12 at one year follow up

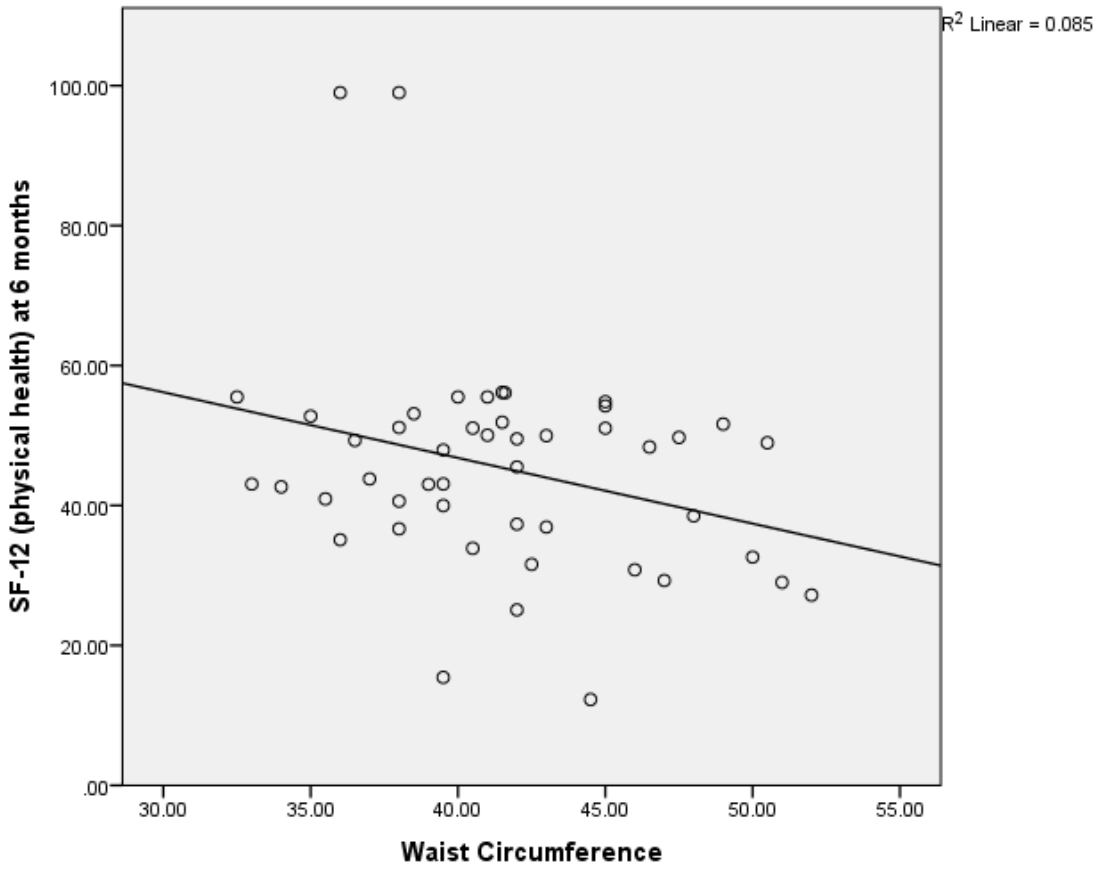

Figure 14 Scatter plot showing relationship between WC (inches) and PCS of SF-12 at six months follow up

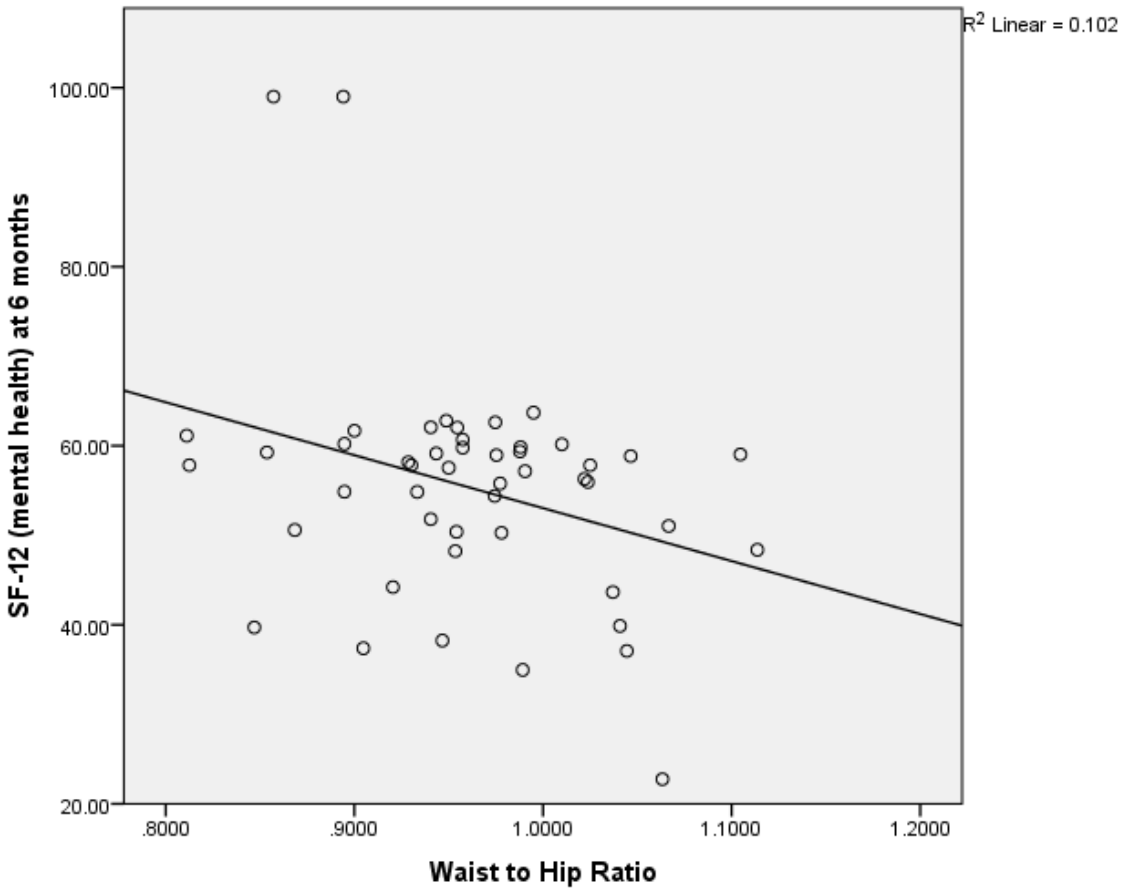

Figure 15 Scatter plot showing relationship between WHR and MCS of SF-12 at six month follow up

7.1.8. Effect of body composition: Between group comparison

The sample was divided into groups based on each body composition measure. Between group differences of outcomes after TKA for each body composition measure was investigated. Figure 8 shows the data analysis methods used to assess the differences.
A high correlation between the baseline scores and follow up scores for the outcomes was observed. In order to control for baseline imbalance between groups, ANCOVA with baseline scores as covariate was used to analyse group differences. After testing for normal distribution of data within each group (normality tables given in Appendix B), ANCOVA was used with baseline score as covariate to assess the differences between groups for the normally distributed data. Non-parametric tests were employed to assess between group differences for data which did not meet the assumptions of ANCOVA. The analysis (ANCOVA) was repeated for each follow up score. Two- way ANOVA was not used because of fewer data in the six months and one year follow up.

BMI groups

The sample was divided into BMI groups based on the already established criteria of non-obese with BMI < 30 kg/$m^2$and obese with BMI $\geq$ 30 kg/m^2.
Group differences for OKS and PCS scores for each follow up time point was tested using ANCOVA. Man Whitney U test was used for MCS and pain scores for each follow up time point.
There seemed to be no effect of BMI on any of the follow up OKS or PCS scores. The covariate, baseline OKS score and baseline PCS score were significantly related to the six month OKS follow up score and six month PCS score respectively ($p < .001$, $p = .002$).
Test statistics for ANCOVA for BMI groups have been given in table 27.
Man Whitney test for BMI group comparison for MCS scores showed no significant differences between BMI groups for any follow up. Also, no significant differences were seen in pain scores between BMI groups before TKA or six weeks after TKA.

Waist circumference groups

Median value of waist circumference (41.5 inches) was used to split the sample into 'low WC' and 'high WC' groups. Thirty one participants were in the low WC groups and 30 were in high WC group.

The six month OKS and PCS score were significantly affected by the covariate (baseline OKS, $p < 0.001$ and baseline PCS, $p = 0.008$). Man Whitney test revealed no significant differences between the low and high WC group for any follow up MCS or pain score (Table 28)

Waist to hip ratio

Median waist to hip ratio (0.95) was used to divide the sample into 'low WHR' group (WHR $\leq$ 0.95, n = 32) and 'high WHR' group (WHR > 0.95, n = 29)

As seen for BMI and WC, no significant effect of WHR was observed on follow up OKS and PCS scores. The six month post-operative OKS and PCS were significantly affected by the covariate i.e., the baseline OKS ($p < 0.001$) and baseline PCS score ($p = 0.004$). Mann Whitney test did not reveal any statistically significant different between groups for MCS or pain scores except, pain score during walking at six week post operation which was significantly greater ($p= 0.02$) in the high WHR group (Table 29)

Body fat percentage groups

The sample was split into two groups using the median BF% (39.9%). There were 30 participants in both groups of 'low BF%' (BF$\leq$ 39.9%) and 'high BF%' group (BF% > 39.9%).

No significant effect of body fat percentage on follow up OKS or PCS was revealed by ANCOVA. Baseline scores however, were significantly low in the 'high BF%' group ($p = 0.003$). Baseline OKS and baseline PCS (covariates) did have a significant effect on the six month OKS ($p < 0.001$) and PCS scores ($p = 0.003$). Man Whitney test for follow up MCS scores or pain scores did not show any significant differences between the BF% groups except for a significantly higher pain scores in the low BF% group for stairs descend at baseline ($p = 0.003$). Test statistics for each analysis is as shown in Table 30.

Ultrasound groups

The sample was categorised into 'low fat thickness' with fat thickness values $\leq$11.167 mm (n = 30) and 'high fat thickness' with fat thickness values > 11.167 mm (n = 31). As seen with previous body composition measures, there was no significant effect of ultrasound measured knee fat thickness on follow up OKS and PCS. The covariate (baseline OKS/PCS) did have a significant effect on the OKS ($p < 0.001$) and PCS scores ($p = 0.002$) at six months follow up. No significant differences were seen between the groups for MCS or pain scores. Test statistics have been given in table.31.

Table 273Between groups comparison for BMI groups

		N	BMI<30	BMI≥30	Test	ES	Sig	Test statistic
OKS	Pre op	61	22.9(6.5)	20.1(5.9)		-0.48		
	6 weeks	61	31.6(8.4)	30.4(10)	ANCOVA	-0.13	0.99	F=.00
	6 months	45	38.1(7.7)	35.3(10.9)	ANCOVA	-0.29	0.89	F = .020
	1 year	32	40.9(5.9)	39.2(7.9)	ANCOVA	-0.25	0.77	F = .087
PCS	Pre op	61	32(8.5)	30.9(6.6)		-0.15		
	6 weeks	60	37.9(10.4)	37.5(9.3)	ANCOVA	-0.04	0.96	F= .003
	6 months	48	46.8(16)	44.4(15.4)	ANCOVA	-0.14	0.95	F= .004
	1 year	32	46.1(7.7)	44.8(10.6)	ANCOVA	-0.14	0.82	F= .054
MCS	Pre op	61	55.4 (38.4)	54.85(42.2)	Man Whitney	-0.17	0.498	U=391.5
	6 weeks	60	54.2 (30.8)	56.7 (46.3)	Man Whitney	0.18	0.403	U =370.5
	6 months	48	57.82(61.62)	56.29(76.24)	Man Whitney	-0.33	0.171	U=210.5
	1 year	32	58.73(31.69)	58.3 (22.21)	Man Whitney	-0.38	0.676	U = 115

Pain rest	Pre op	59	3.7 (9)	2.95 (8.2)	Man Whitney	0.11	0.646	U =84.5
	6 weeks	59	1.35 (7.1)	1.2 (9.4)	Man Whitney	0	0.838	U = 394
Pain walking	Pre op	59	7.5 (5.7)	7.45 (6.74)	Man Whitney	-0.27	0.437	U = 364
	6 weeks	59	1.5 (5.2)	2.2 (9)	Man Whitney	0.39	0.149	U =315.
Pain stair climb	Pre op	59	6.8 (6.2)	7.5 (9.6)	Man Whitney	-0.34	0.405	U = 360
	6 weeks	59	1.35 (7.70)	2 (9.4)	Man Whitney	0.23	0.419	U = 355
Pain stair descend	Pre op	55	8.55(7.2)	7.9 (8.4)	Man Whitney	-0.37	0.229	U = 293
	6 weeks	58	1.9 (9)	2.3(9)	Man Whitney	0.12	.619	U = 365

Mean (standard deviations) shown for OKS, PCS. Median (inter quartile range) shown for MCS and pain scores**.**

Table 28 Between groups differences for WC groups

		N	Low WC ≤ 41.5 inches	High WC > 41.5 inches	Test	Sig	Test statistic
OKS	Pre op	61	22.7(6.3)	19.5(5.8)			
	6 weeks	61	31.2(8.1)	30.5(10.6)	ANCOVA	0.8	F=3.94
	6 months	45	38.5(7)	34(11.8)	ANCOVA	0.66	F=0.20
	1 year	32	41.7(5.8)	37.4 (8)	ANCOVA	0.15	F=2.19
PCS	Pre op	61	33(8)	29.5(6.2)			
	6 weeks	60	38.3(10.1)	37(9.3)	ANCOVA	0.85	F=0.04
	6 months	48	9.5(17.1)	40.5(12)	ANCOVA	0.24	F=1.42
	1 year	32	47.8(7.3)	41.8(11)	ANCOVA	0.16	F=2.08
MCS	Pre op	61	56.3(39.8)	54.6(41.2)	Man Whitney	0.34	U=399
	6 weeks	60	53.4(30.8)	56.7(46.3)	Man Whitney	0.32	U=382
	6 months	48	58(61.6)	55.9(39.3)	Man Whitney	0.1	U=206
	1 year	32	59.6(31.7)	57.8(10.4)	Man Whitney	0.94	U=121

Pain rest	Pre op	59	3.7(9)	3(8.2)	Man Whitney	0.55	U=394.5
	6 weeks	59	1.3(7.1)	1.3(9.4)	Man Whitney	0.92	U=428.5
Pain walking	Pre op	59	7.3(7.6)	7.6(7.3)	Man Whitney	0.89	U=425
	6 weeks	59	1.6(7.9)	2.4(9)	Man Whitney	0.24	U=358
Pain stair climb	Pre op	59	7(7.8)	7.7(9.6)	Man Whitney	0.69	U=408
	6 weeks	59	1.4(7.7)	2.4(9.4)	Man Whitney	0.20	U=351
Pain stair descend	Pre op	55	8.2(8.1)	7.9(7.1)	Man Whitney	0.69	U=351.5
	6 weeks	58	1.8(9)	3.5(9)	Man Whitney	0.39	U=365.5

Mean (standard deviations) shown for OKS, PCS. Median (inter quartile range) shown for MCS and pain scores**.**

Table 29 4Between groups differences for WHRgroups with mean (SD) for ANCOVA and median (range) for Mann Whitney tests

		N	Low W $\leq$ 0.95	High WH > 0.95	Test	Sig	Test statistic
OKS	Pre op	61	21.8(5.7)	20.4(6.8)			
	6 weeks	61	31.8(7.9)	29.8(10.7)	ANCOVA	0.51	F=.447
	6 months	45	37.4(7.2)	5.4(11.7)	ANCOVA	0.9	F=0.02
	1 year	32	39.3(7.3)	40.7(6.8)	ANCOVA	0.6	F=.28
PCS	Pre op	61	31.9(6.8)	30.6(8)			
	6 weeks	60	40.1(8.6)	5.1(10.2)	ANCOVA	0.85	F=.04
	6 months	48	48.4(17.4)	42.3(13)	ANCOVA	0.24	F=1.42
	1 year	32	46.6(9.3)	44.3(9.5)	ANCOVA	0.16	F=2.08
MCS	Pre op	61	55.3 (39.8)	54.7(41.2)	Man Whitney	0.58	U=425.5
	6 weeks	60	54.2(29.8)	56.7(46.3)	Man Whitney	0.19	U=360
	6 months	48	57.8(61.6)	56.7(40.9)	Man Whitney	0.42	U=249

	1 year	32	57.8(26.8)	59.2(31.1)	Man Whitney	0.52	U=111
Pain rest	Pre op	59	3.5(9)	3(8.2)	Man Whitney	0.9	U=425.5
	6 weeks	59	1(7.1)	1.4(9.4)	Man Whitney	0.31	U=368.5
Pain walking	Pre op	59	7.4(7.7)	7.6(7.2)	Man Whitney	0.95	U=430
	6 weeks	59	1.5(7.9)	2.8(9)	Man Whitney	0.02	U=285
Pain stair climb	Pre op	59	7(9.6)	8(7.7)	Man Whitney	0.81	U=418.5
	6 weeks	59	1.5(7)	2.5(9.4)	Man Whitney	0.06	U=309.5
Pain stair descend	Pre op	55	7.8(8.1)	8(5.6)	Man Whitney	0.09	U=274.5
	6 weeks	58	1.9(9)	3.9(9)	Man Whitney	0.31	U=355.5

Mean (standard deviations) shown for OKS, PCS. Median (inter quartile range) shown for MCS and pain scores**.**

Table 30 Between group comparison for BF% groups

		N	Low BF% ≤ 39.9%	High BF% > 39.9%	Test	Sig	Test statistic
OKS	Pre op	61	20.2(6.7)	22(5.7)			
	6 weeks	61	30.9(9.6)	30.8(9.3)	ANCOVA	0.73	F= .117
	6 months	45	36.4(11.1)	36.2(9)	ANCOVA	0.41	F=.702
	1 year	32	41.8(6.3)	38.7(7.4)	ANCOVA	0.26	F=1.3
PCS	Pre op	61	29.7(7.2)	32.9(7.4)			
	6 weeks	60	37.6(10.4)	38(9.2)	ANCOVA	0.87	F=.029
	6 months	48	44(11.4)	46.4(18.8)	ANCOVA	0.88	F=.024
	1 year	32	47.6(7.7)	43.8(10.2)	ANCOVA	0.17	F=1.986
MCS	Pre op	61	54.5(38.40)	55.9(44.2)	Man Whitney	0.53	U= 407
	6 weeks	60	54.2(37.9)	57.7(44.7)	Man Whitney	0.54	U=395
	6 months	48	57.3(40.9)	57.8(64)	Man Whitney	0.54	U=246
	1 year	32	58.8(31.1)	57.8(26.8)	Man Whitney	0.86	U=119

Pain rest	Pre op	59	3(9)	3.2(7.1)	Man Whitney	0.91	U=413
	6 weeks	59	1.3(8)	1.4(9.4)	Man Whitney	0.95	U=416.5
Pain walking	Pre op	59	7.8(5.9)	7.1(7.7)	Man Whitney	0.11	U=316.5
	6 weeks	59	2(8)	2(9)	Man Whitney	0.46	U=372.5
Pain stair climb	Pre op	59	7.5(7.7)	7.4(9.6)	Man Whitney	0.42	U=369
	6 weeks	59	2.2(9.4)	1.9(9.3)	Man Whitney	0.66	U=392
Pain stair descend	Pre op	55	9(7.5)	7.5(8)	Man Whitney	**0.003**	U=190.5
	6 weeks	58	2.5(9)	2.3(9)	Man Whitney	0.74	U=385

Mean (standard deviations) shown for OKS, PCS. Median (inter quartile range) shown for MCS and pain scores.

Table 31 Between group differences for US groups

		N	Low fat thickness≤ 11. 167 mm	High fat thickness> 11.167 mm	Test	Sig	Test statistic
OKS	Pre op	61	21.7(7.1)	20.5(5.3)			
	6 weeks	61	31.6(9.8)	30.2(8.9)	ANCOVA	0.67	F= 0.18
	6 months	45	38.1(10.5)	34.8(9.1)	ANCOVA	0.38	F=0.782
	1 year	32	42.5(6.7)	37.7(6.7)	ANCOVA	0.13	F=2.383
PCS	Pre op	61	31.4(8.6)	31.2(6)			
	6 weeks	60	39.1(11.1)	36.3(8)	ANCOVA	0.25	F=1.323
	6 months	48	46.5(17.3)	44.2(14)	ANCOVA	0.50	F=0.474
	1 year	32	48.1(9.2)	42.9(9)	ANCOVA	0.19	F=1.832
MCS	Pre op	61	53.6(12.4)	49.4(11.3)	Man Whitney	0.08	U=342.5
	6 weeks	60	52.6(9.3)	50.7(12.1)	Man Whitney	0.73	U=427
	6 months	48	55.8(13.5)	54.9(12.5)	Man Whitney	0.70	U=268.5
	1 year	32	55.7(8.8)	53.2(9.4)	Man Whitney	0.64	U= 115

Pain rest	Pre op	59	3.4(2.6)	3.7(2)	Man Whitney	0.39	U =378.5
	6 weeks	59	1.7(2)	2.1(2.2)	Man Whitney	0.35	U = 373.5
Pain walking	Pre op	59	7.1(1.5)	6.7(2.2)	Man Whitney	0.81	U = 419
	6 weeks	59	2.5(2.2)	2.5(2.1)	Man Whitney	0.73	U = 412
Pain stair climb	Pre op	59	7.1(2)	6.8(2.4)	Man Whitney	0.84	U = 422
	6 weeks	59	2.9(2.9)	2.6(2.4)	Man Whitney	0.99	U = 434
Pain stair descend	Pre op	55	8(1.9)	6.9 (2.4)	Man Whitney	0.05	U = 261
	6 weeks	58	3.3(3)	3.3(2.7)	Man Whitney	0.82	U = 405.5

Mean (standard deviations) shown for OKS, PCS. Median (inter quartile range) shown for MCS and pain scores**.**

7.1.9. Section summary

To assess the influence of obesity on TKA self-report outcomes, body composition of patients was measured before their TKA operation and self-report outcome data was collected at baseline (pre operative), six weeks post-operatively, six months post-operatively and one year post-operatively. The hypothesis was addressed in two ways, firstly, by exploring the influence of obesity on the TKA outcomes using correlation analysis and secondly, by assessing the difference in outcomes between body composition groups.

The correlation analysis to explore the influence of obesity on TKA outcomes revealed that of the five body composition measures, BMI and waist circumference had a significant negative relationship with OKS score at six months follow up and also with OKS score at one year follow up. This indicated that at six months and one year after a TKA, patient perceived knee function was poorer as BMI increased. Similarly, increasing waist circumference also indicated a poorer knee function at six months and one year after TKA. The overall health related physical function measured by PCS was significantly related to BMI at one year and to wait circumference at six months after TKA.

Between group comparison with ANCOVA (controlling for baseline score) revealed no significant group differences for knee function or overall physical health between obese and non-obese categorised by any of the body composition measures for any given time point. Non- parametric tests also revealed no group differences for overall mental health and pain scores for any body composition measures at any time point except pain during walking at six weeks follow up, which was greater in the 'high WHR' group than the 'low WHR' group.

The influence of BMI and waist circumference observed in the correlation analysis was not reflected when group differences were assessed. After controlling for baseline scores with ANCOVA, it was observed that there was no difference in the knee function or overall physical function between obese and non-obese group categorised by BMI values for any of the follow up times. Similarly, no differences were seen between the waist

circumference groups for these outcomes at any follow up period. Some explanation maybe offered by the scatter plots for these outcomes as the region before and at the cut off point for grouping show similarly spread values and therefore no clear relationship between variables. However, with greater BMI or WC, some extreme outcomes values pulled the relationship to a significant level.

7.2 Discussion

7.2.1. Section overview

This section discusses the methodology used and the findings of the study assessing the effect of obesity on TKA outcomes. The section begins with a summary of key findings. The measurement and findings of body composition methods is discussed followed by measurement of primary and secondary outcome measures. Findings of the current study have then been compared with those of previous studies assessing the effect of obesity on TKA outcomes. By illustrating the various theories behind a possible or no effect of obesity, the chapter then addresses the question: is it weight or fat that affects the outcomes? Finally, a summary of the section is presented.

7.2.2. Summary of key findings

The aim of the study was to assess the effect of obesity on self-report outcomes after total knee replacement. The alternate hypothesis for the study that obesity resulted in poorer outcomes after total knee replacement was rejected and the null hypothesis that obesity has no effect of self-report outcomes after total knee replacement was retained

The hypothesis was tested using two different types of statistical analysis in order to answer the research question: Firstly, correlation analysis and scatter plots were used to address the influence of obesity on total knee replacement and secondly, statistical tests for between groups differences were used for group comparison of outcomes between various body composition groups. The key findings of the two analyses are given below.

Correlation analyses

Obesity had no influence on any of the reported outcomes six weeks after surgery. For outcomes six months and one year after surgery a negative correlation was seen with BMI, WC and WHR. It was observed that increasing BMI corresponded to poorer patient reported knee function at six months and one year after surgery and also poorer overall physical function an year after surgery. Increasing WC corresponded to poorer patient reported knee function at six months and one year after surgery and also poorer overall physical function six months after surgery. The reported overall mental health was not affected by any of the body composition measure except a negative correlation with WHR six months after surgery. However, the scatter plots of these relationships showed that most data points were clustered around a small range of body composition measures with a few extreme values resulting a significant correlation coefficient, For example, most values were clustered between the BMI values of 25 kg/m^2 and 35 kg/m^2 (between 35 inches and 45 inches for WC and between 0.9 and 1.05 for WHR) with no clear association with the outcomes. However, after checking for outliers, few extreme values (one to four) at the higher end of the body composition measure indicating high obesity with poor outcome resulted in significant correlations. The significant correlation between WC and six month PCS and WHR and MCS at six months were observed to be because of two very high values of PCS and MCS with lower WC (<40 inches) and WHR (<0.90).

Analysis of between group differences

The effect of body composition on the few outcomes as shown by the correlation analysis were not reflected in the between group comparisons. No differences were found between the body composition groups for patient reported knee function and overall quality of life after total knee replacement. Significant greater pain during walking six weeks after surgery in patients with WHR > 0.95 was observed, but no statistically significant difference were seen between any of the body composition groups for pain at rest, during

stair climbing or during stair descending. The between group values of stair climbing at six weeks also showed greater pain in the obese groups categorized by WHR (with effect sizes of 0.64) but this was not seen to be statistically significant. Hence it likely that the current study was not appropriately powered to detect statistically significant differences between the body composition groups.

7.2. 3. Measurement of body composition

As discussed in Chapter 6, five different methods of measuring body composition which measure different aspects of anthropometry were used in the study and these included: Body Mass Index (BMI), Waist Circumference (WC), Waist to Hip Ratio (WHR), Bioelectrical Impedance Analysis (BIA) and Ultrasonography (US)

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Obesity classification and cut off values

As seen in section 8.1 (results), the data from these measurement methods were analyzed both as continuous data and also by using cut off values to classify the data into obese and non-obese groups.

In general the most widely reported method of measuring obesity in the orthopaedic literature is BMI and more specifically, with regard to the effect of obesity on total knee replacement outcomes, only the effects of body weight and BMI have been explored. Body mass index is extensively used not only in epidemiological studies but also in clinical practice. The BMI classification of obesity as recommended by the WHO (World Health Organization) 1995 report is now used as the reference criteria for classifying obesity. Classification of obesity based on BMI in this study has been based on this established reference criteria (BMI $\geq$ 30 kg/m^2 as obese). Apart from categorizing patient obesity based on an established reference, this also allowed comparison of the data from the current study with previous literature. Reference cut off values for obesity classification have also been recommended for WC, WHR and BIA, however, no known classification exists for regional obesity measured using ultrasonography. Therefore, a median split technique was employed on ultrasonography values to categorize patients into obese and non-obese. The 2000a WHO report recommends cut off values of WC > 102 cm (men) and >88 cm (women) and WHR > 0.90 cm and > 0.85 cm for a substantially increased risk of metabolic complication. The rationale for these cut off points for WC and WHR were based the increased relative risk of metabolic disease

resulting from abdominal obesity observed in a study on a random sample of 2183 men and 2698 women in Netherlands (Han et al. 1995) and not on the methods' prediction of the amount of abdominal adipose tissue (WHO 2000a report). On applying these cut off values of WC and WHR to the current study data, it was found that of the 23 patients considered non-obese according to BMI (BMI <30 kg/m^2), 10 (43%) of these 23 were at a 'substantial risk of metabolic complications' according to WC criteria (WC > 102 cm (men) and >88 cm (women) while 17 (74%) were at a 'substantial risk of metabolic complications' according to WHR criteria (WHR > 0.90 cm and > 0.85 cm). While this could show underestimation of obesity by the BMI criteria, using the WC and WHR cut off to the current study's data lead to a wide disparity between the group sizes (14 vs. 47 for WC groups and 7 vs. 54 for WHR groups) making the results of statistical analysis clinically meaningless. So, instead a median split technique was used on WC and WHR data to form obese and non-obese groups for statistical analysis.

At present no evidence-based established cut off values for percentage body fat exist (Oreopoulos et al. 2011). Many studies have used a cut-off points of total body fat percentage > 25% in males and total body fat percentage > 30% in females with reference given to the WHO 1995 report. However it was noted in published correspondence to the editor (Mayo journal proceedings 2011) that these values were not recommended by WHO 1995 report but the guidelines of the American Association of Endocrinology. However, no evidence-based rationale was actually provided for these cut off points (Ho Pham and Campbell 2011). Gallagher et al. (2000) considered the effect of age, sex and race on total body fat percentage and developed cut offs based on BMI classification as total body fat percentage $\geq$ 31% (males) and $\geq$ 43% (females) corresponding to BMI $\geq$ 30kg/m^2 for the age range of 60-79 years. Using these cut offs on the current study's data, ten patients with BMI <30 kg/m^2 (non-obese) were above the total body fat percentage cut off thus indicating an underestimation of obesity by BMI as seen with WC and WHR. Or overestimation of obesity using these cut-offs of body fat.

Assessment of body composition

Anthropometric measures of obesity which include BMI, WC and WHR remain the most widely used measures of obesity in epidemiological research and clinical practice because of their practicability and ease of use and their correlation with body fat. Several studies have shown a good correlation of BMI with body fat percent (Khaodiyar and Blackburn 2001; Prentice and Jebb 2001; Frankenfield et al. 2001). WC and WHR being indirect measures of central obesity have shown to be correlated with abdominal fat (Chan et al. 2003) although WHR is seen more as a measure of the type of body fat distribution.

Being widely used for population studies, BMI has the advantage of having extensive reference data and established relations with body fat and morbidity and mortality (WHO 1995 report). By its correlation to body fat, BMI givens indices of the level of obesity, but it does not distinguish between the fat and the lean mass which contribute to the body mass (Khaodiyar and Blackburn 2001; Prentice and Jebb 2001; Frankenfield et al. 2001). Moreover, the reference data (cut off points) for BMI are the same for all age, gender and race thus do not account for the influence of these factors on obesity (Jackson et al. 2002). With increasing age, there is conversion of lean mass into fat mass and therefore for a given body mass, an older person will have a higher fat mass (Smalley et al. 1990; Prentice and Jebb 2001; Snijder et al. 2006). While a good correlation between BMI and BF% was seen in the present study data ($r^2 = 0.42$, $p<0.001$), some effect of age and gender was seen leading to disparity between body fat and BMI. For example, a BMI of 49.1 in a 63 year old female patient corresponded to a body fat % of 54.8% which was less than that of two other female patients of BMI 46.2 (age = 70 years) and 44.9 (age = 69 years) had BF% of 57.25 and 55.08% respectively. For lower BMI's, a female patients aged 89 years with a BMI of 21 corresponded to BF% of 33.5% while a male patient aged 74 years with a BMI of 23 corresponded to BF% of 19.6%. Effect of ethnicity on BMI as suggested by Jackson et al. (2002) is not applicable in this study as all patients in the study sample were Caucasians.

Measurement of body fat by BIA is considered more accurate than the above anthropometric methods (Gray et al. 1989). While its ease of use add to its advantages, the interpretation of highly obese subjects (BMI >34 kg/m^2) is to be treated with caution as in these patients the total body water and extracellular water is relatively higher leading to an overestimation of fat free mass and underestimation of fat mass. (Kyle et al. 2004).

We estimated regional distribution of fat using WC and WHR for central obesity and US for measuring fat thickness above the knee. Echo patterns in ultrasonography images quantitatively differentiate tissue which allowed us to clearly see the muscle-fat interface. While there is evidence that ultrasound measurement of subcutaneous fat particularly over quadriceps can be used to predict total body fat in Caucasians (Weits et al. 1986; Fanelli and Kuczmarski. 1984), this was not attempted in this study.

Practical considerations for measurement of body composition

Anthropometric measurement errors are unavoidable and therefore the standardization of measurement method should be closely followed for this. While close attention can be paid to examine participants for research purposes with a limited number of observers, the standardization of measurement methods is more difficult in a regular clinical setting. In a review Ulijaszek and Kerr (1999) concluded that weight and height are most accurate and repeatable while waist and hip circumferences show inter observer differences. The ease of standardizing the measures of boy mass and body height makes BMI the most appropriate body composition measure in a clinical setting. Although change in scales, different rounding of numbers by different assessors may lead to some variation but not a drastic difference in BMI values as it would be with any other measurement.

Various measurement protocols for waist circumference have been recommended by health authorities of which the three most common are: 1) at the level of umbilicus 2) minimal waist and 3) mid-point between lower border of ribcage and iliac crest. However there is no consensus regarding the optimal protocol for measurement and no rationale has been given for any recommendations (Ross et al. 2007). A systematic review of 120

studies conducted by an expert panel concluded that the measurement protocol had negligible influence on the relationship between waist circumference and morbidity and mortality (Ross et al. 2007). The panel recognized that protocols using bony landmarks would seem optimal as they would minimize measurement error, will be transferable to clinical practice and allow easy self measurement. The method recommended by WHO (2000) measuring waist circumference as mid-point between lower border of ribcage and iliac crest was chosen in this study as it allowed to better standardize the circumference measurement especially in obese patients with significant abdominal folds and use the WHO (2000) recommended cut offs for waist and hip circumference for assess data. Waist and hip circumferences was observed in this study to be simple to measure and standardize. Although a tendency for either pulling in abdominal muscles or forced expiration by participants during measurement was observed, this could be rectified with appropriate instructions to the participant. Standardization of the measurement was further ensured as only one observer was taking the measurements for the study although in a clinical setting where it is more likely that there is more than one observer, reliability may be more difficult.

Standardization of measurement among the five methods used was most difficult for BIA. Maintaining the similar testing conditions for BIA is essential for accurate and reliable measurements. Lack of maintaining these conditions would affect the subsequent calculation from predictive equation resulting in differences in reading (Kushner et al. 1996). Testing conditions prescribed by the manufacturer were followed for accurate calculation of predictive equations used by the manufacturer (Maltron Ltd.). Fasting condition required before BIA measurement (as described in Chapter 6) was the most difficult to maintain especially since the baseline assessment was at the time of the patient's pre admission clinic appointment which in practice can take even up to three hours. While it was attempted to keep these conditions by adjusting assessment times, it would be impossible to manage these conditions in a busy clinic.

The above measurement methods require no or minimal training, however, ultrasonography did require training and testing for reliability before application in the study. Position of the leg had to be considered carefully before measurements. It was

observed that keeping knee in a slight flexion (approximately40 degrees) position allowed adequate relaxation of the quadriceps muscle so that the contraction did not compress other tissues and the thigh folds above the knee (especially in obese) did not hinder probe placement. Minimal compression of tissues due to the pressure applied by the ultrasound probe had to be considered. Consistency of probe placement and pressure applied was achieved with training.

7.2. 4 Outcomes measure

Oxford knee score

Oxford knee score was originally developed for use in randomized controlled trials but since its development, it has been used extensively in cohort studies and audits. Its simplicity and brevity allows for a higher completion rate than other measures (Dawson et al. 1998; Dunbar et al. 2001). At baseline assessment, when the assessor was present during OKS completion, it was observed that patients found the questionnaire easy to complete. This was also reflected in the 95% response rate for a completed questionnaire at six weeks post-operatively. The completion rates at the longer follow up of six months and one year were considerably lower (70% and 50% respectively) than previous studies with completion rates ranging from 81% - 89% (Whitehouse et al. 2005; Dunbar et al. 2001). The six weeks questionnaire were completed by patients either in the presence of an assessor or via post with telephonic reminders, whereas, the six months and one year scores were obtained from the hospital database. It is likely that this difference in the method of data collection affected the response rate at six months and one year.

Patients in this study found the OKS simple but some did require clarification for item 7 of the questionnaire ‘Could you kneel down and get up again afterwards?’ as they believe they should not or had never attempted to. This issue was also raised by Whitehouse et al. (2005) in their study where patients selected the last response (no impossible) even when

they scored well in other items and hence the item was criticized for being inappropriate. The authors of OKS have emphasized that the 'Could' in the question is highlighted to indicate a hypothetical situation of kneeling. Although this had to be clarified in some cases, it is believed that it did not affect the results of the study.

The original OKS scoring system had total scores ranging from 12 (best outcomes), to 60 (worst outcomes). With criticism of this scoring system as being unintuitive, these scores were later modified by the authors to a scoring system which produced overall scores ranging from 0 (worst outcome) to 48 (best outcomes) (Murray et al. 2007). Applying the new scoring system (0-48), the mean pre operative score for this study was 21.1± 6.2, at six weeks was 31±9.3, at six months was 36.3± 9.8 and at one year was 40± 7. These scores were slightly better than those presented by Murray et al. (2007) (pre operative mean = 18±7.5 and one year mean = 34.2± 10) and recently by Judge et al. (2012) (pre operative mean = 20± 8 and one year mean = 34.5± 9.1).

According to Murray et al. (2007), due to the symptom severity pre operatively and milder symptoms at follow up, the OKS scores tend to be skewed, to the left i.e., lower scores pre operatively and skewed to the right post-operatively. In this study, normal distribution for pre operative scores was observed which indicate that some patients had only mild symptoms pre operatively. The pre operative scores ranged from as low as 9 to 36. This raises the question of why patients with mild symptoms were operated at all; however, there may be other baseline clinical characteristics to be considered such as radiological severity (Dieppe et al. 1999). O'Neill et al. (2007) in a qualitative meta-synthesis further point towards the complexity of decision making involved in an elective procedure like TKA which are influenced by factors such as social and cultural circumstances and motivation.

Finally, the measurement of outcomes goes beyond the assessment of the statistical significance of the change in scores to determining the real clinical and subjective meaning of the scores. One method of assessing a clinically meaningful difference is using the Minimal Clinically Important Difference (MCID) which is defined as the smallest difference in score which patients perceive as a meaningful change (Jaeschke et al. 1989). The MCID for Oxford scores is not yet established. Although the authors

suggest it between three and five points, it is cautioned that it could be lower than three points (Murray et al. 2007). In order to interpret the meaning of the scores as good or bad outcomes, attempts have been made to dichotomize or categorize data from patient reported outcomes measures. A recent attempt by Judge et al. (2012), describe how patient acceptable symptom state (PASS scores) can be used to create thresholds for change scores (pre-operative to six months) and absolute score at six months which relate to the patients satisfaction with the surgery or in other words, the minimal value of OKS beyond which patients consider themselves in a satisfactory state of wellbeing. They identified a threshold score of 11 for change score and 30 for absolute score beyond which patients achieved the highest satisfaction with surgery. However, external validation of these thresholds is required for its general implementation in practice. Judge et al. (2012) recognize that the threshold scores vary with the pre operative or baseline scores and that different threshold scores will be needed to define outcome according to baseline scores. Applying this threshold to six month follow up data of this study, 80% patients had a score >30, i.e., 80% of the study sample achieved the highest satisfaction levels with surgery. However, in this study, separate measurement of satisfaction data was not collected to compare with the results by Judge et al. (2012).

Short Form 12

Patients reported the same level of simplicity and brevity with completing SF12 as they did with OKS. This was reflected in the similar response rate of SF12 (93.8% at 6 weeks, 75% at six months and 50% at one year post op). As with OKS, six month and one year follow up response was considerably lower than the 87.3% seen in a previous study with by Dunbar et al. (2001).

In a SF12 cross validation study by Gandek et al. (1998), SF12 scores were obtained from national representative samples of nine countries from which mean PCS and MCS scores obtained from UK population for the age range 65-74 years were 45.3± 11.2 and 53.2± 9.1. They concluded that PCS scores declined with age while MCS scores remained stable or even increased with age. This was also seen true for this sample which was of a

higher age group (mean age = 70.6 years). PCS scores for our sample was lower than the population score (age 18 to 74 years) of 50.9±9.4 even at one year after surgery (at one year, mean = 45.3± 9.3) while MCS scores were at par with that of the population and even better at follow ups (at one year, mean = 58.3±9.4). Comparing the current data with primary TKA population, scores were higher than that seen by Hartley et al. (2002) at six months (45.3 vs. 40.8) and one year (45.3 vs. 41.1) after surgery. The higher scores in this study sample for OKS and SF12 compared could be a resultant of the lower level of response to follow up in our study (50% at one year). A low level of follow up can be a limiting factor as it has been suggested that patients who do not respond to questionnaires have poorer functional outcomes (Kim et al. 2004) and are more dissatisfied with their TKA (Robertsson and Dunbar 2001)

The influence of comorbidity and disease at other joint poses another challenge for all patient reported outcomes measures. Twenty three percent of the patients in this study suffered from other joint problems; four of these had previous total hip replacement (Table 17, Section 8.1.3) and 28% had had a previous TKR on the contralateral limb. Oxford knee score attempts to focus solely on function at the knee with specific questions related to the knee, in order to enhance specificity in the TKA population. On comparison with SF36, OKS was seen to be more sensitive to change than SF36 (Dawson et al. 1998).To accommodate the complex nature of patients' health problems, authors of OKS recommend the use of a validated generic questionnaire in addition to the knee specific OKS (Dawson et al. 2006). While the correlations between OKS and PCS for the corresponding time point were high ($p<0.01$), the greater effect size of OKS compared to that obtained with PCS (ES for the total sample for change from baseline to six months = 2.45 vs. 1.9 and ES for change from baseline to one year = 3.14 vs. 1.9) indicates that in this study OKS was more sensitive to change at follow up than PCS. This highlights that OKS, as expected, was more sensitive to detect improvement or deterioration in this TKA sample while the generic SF12 could have been more susceptible to influences from other joints or comorbidity.

7.2. 5 Effect of obesity on patient reported outcomes: Comparison with previous evidence

This study is different from previous studies in that it is the first study to assess the effect of four other measures of obesity along with BMI on patient reported outcomes following TKA. Furthermore, this is the only study using OKS questionnaire as a patient reported outcome assessing the effect of obesity. Therefore, in this section comparison has been attempted between the current study results of BMI groups with previous studies reporting patient reported outcome measures, although different from OKS.

The knee specific patient reported outcome measure of choice for most studies seems to be WOMAC. Among the more generic patient reported outcome measures, SF36 was the questionnaire of choice in most studies. A few studies have assessed outcome using the SF12 questionnaire (Rajgopal et. al 2008; Dowsey et al. 2010).

Knee function; Change scores

The three studies assessing change/improvement in WOMAC from pre operative to one year after surgery between BMI groups observed no significant difference between BMI groups (Stickles et al. 2001; Rajgopal et al. 2008; Nunez et al. 2010). This concurred with the finding of no significant difference between the BMI groups for change in OKS from pre operative to one year post surgery in this study (mean = 16.6$\pm$ 5.4 for non-obese group and 17.7$\pm$9.3 for obese group). These studies used different cut off points to define BMI groups. While Stickles et al. (2001) used five BMI groups (< 25 kg/m^2 as healthy; 25 to 29.9 kg/m^2 as overweight; 30 to 34.9 kg/m^2 as class I obese; 35 to 39.9 kg/m^2 as class II obese; and $\geq$ 40 kg/m2 as class III obese BMI $\geq$ 30 kg/m^2), Nunez et al. (2010) defined BMI $\geq$ 35 kg/m^2 as 'severely obese' comparing it with BMI < 35 kg/m^2 and Rajgopal et al. (2008) defined BMI $\geq$ 40 kg/m^2 as their 'morbidly obese' group

comparing it with BMI < 40 kg/m^2. Thus, this lack of effect of BMI groups on patient reported knee specific function seemed to be irrespective of the cut off points used for BMI grouping. However, the change in KSS function scores (part of KSS scored by patients, it includes three questions each on walking ability, stairs and use of walking aid) was observed to be lower i.e., worse in patients with BMI $\geq$30 kg/m^2 at one year after surgery by Dowsey et al. (2010).

Knee function; Absolute scores

On assessing absolute OKS score at one year after surgery, no differences were observed between groups (BMI $\geq$30 kg/m^{2}or BMI <30 kg/m^2) after controlling for pre operative OKS score. Conflicting results were however seen in the between group analysis of absolute WOMAC scores at one year after surgery between studies. A poorer KSS function score in obese (BMI $\geq$30 kg/m^2) was seen at one year follow up by Dowsey et al. (2010). Rajgopal et al. (2008) using BMI $\geq$40 kg/m^2 or <40 kg/m^2 classification for grouping reported lower one year post-operative WOMAC score in morbidly obese. Pre operative OKS score was not significantly lower in obese in the current study's sample. Lower pre operative scores were also observed by Rajgopal et al. (2008) in their study. On the other hand using a classification of BMI $\geq$35 kg/m^2 or <35kg/m^2, Nunez et al. (2010) saw no differences between groups in their post-operative one year WOMAC score. One of the factors affecting post-operative score considerably is the pre operative score. In the current study this has been controlled for by using the pre operative score as a covariate in the ANCOVA. Nunez et al. (2010) controlled for the pre operative measure by using a matched control group, however, the pre operative WOMAC stiffness scores in the study were poorer for the obese group. While the two above studies with lower absolute post-operative score at one year (Dowsey et al. 2010; Rajgopal et al. 2008) did not control for pre operative scores.

BMI as a continuous variable vs. Knee function

BMI as a continuous variable had a significant negative correlation with six month and one year post-operative OKS in this study ($r = -0.34$, $r = -0.42$ respectively). A significant negative correlation was also seen between BMI and one year WOMAC scores ($p < 0.01$, no r value given) by Stickles et al. (2010). A negative effect of BMI $\geq$ 40 kg/m^2 on one year WOMAC was reported by Rajgopal et al. (2008) in their regression model (b coeff = -5.2, $p = 0.027$) and on the other hand, using regression models with BMI as one of the predictors, Escobar et al. (2007) concluded that BMI did not predict worse outcomes measured by WOMAC and SF36 six months after surgery.

Overall physical health

Change score for PCS showed no significant difference between BMI groups (mean = 13.1 $\pm$ 11 for non-obese and 13.5$\pm$10 for obese). This result was also observed by two other studies which assessed the SF12 as an outcome measure with follow up of up to one year after surgery (Rajgopal et al. 2008; Dowsey et al. 2010). However, the current study found no significant difference between the BMI groups for absolute one year PCS scores while controlling for pre operative scores. Dowsey et al. (2010) and Rajgopal et al. (2008) observed significantly poorer one year PCS score in their morbidly obese groups. Considering that SF12 is derived from SF36 and has similar domains and scoring system, comparison can also be made between the SF12 results in this study with the results those assessing SF36 (Stickles et al. 2001; Steven-Lapsley et al. 2010). Change in SF36 from pre operation to one year post operation was not different between five BMI groups (Stickles et al. 2001) which reflect the current study's findings of no difference in the overall quality of life, specifically in the physical domain.

BMI as a continuous variable vs. SF12

Using BMI as a continuous variable for the analysis of PCS scores, this study observed a weak but significant negative relation between BMI and the one year PCS ($r = -0.37$, $p =$

0.04). This negative relation of BMI was also seen with PCS of SF36 ($p = 0.02$) in the study by Stickles et al. (2010). However when used in regression models as a predictor, BMI did not seem to account significantly to the variation in SF36 up to one year after surgery in other studies (Escobar et al. 2007, Steven-Lapsley et al. 2010).

The current study found no significant relation between BMI and MCS of SF12 and neither any group differences in change of MCS from pre operative to one year after surgery or absolute MCS score at one year after surgery. Lack of an effect of BMI on MCS was also seen in Dowsey et al. (2010) and Stickels et al. (2001) (MCS of SF36). Poorer MCS absolute scores pre operatively and at one year for BMI $\geq$ 40 kg/m^2 were seen by Rajgopal et al.(2008), however, greater improvement (change score) was seen in MCS for these morbidly obese patients.

Pain scores

Pain at the knee (at rest, during walking, stair climbing and stair descending) measured on a VAS scale was not significantly different between BMI groups as absolute one year scores or as change scores from pre operatively to follow up. This was similarly seen by Naylor et al. (2008) who used a VAS pain scale on a sample including both knee and hip replacement patients. Nunez et al. (2010) also did not see a difference between their BMI groups (BMI $\geq$ 35 kg/m^2 and BMI < 35 kg/m^2) for WOMAC pain scores. A ten point VAS pain scale used by Namba et al. (2005) indicated greater pain relief in obese (BMI $\geq$35 kg/m^2) from baseline to one year after surgery.

In summary, improvement in the knee related physical function and overall physical function as reported by patients was similar in all TKA patients irrespective of their BMI group or the classification used to categorize patients into obese and non-obese groups. Disparity in findings emanates from literature when analysis is done using absolute scores or when using BMI as a continuous variable.

The current study did not see any difference in physical function scores between obese and non-obese at one year after operation and neither did studies by Stickles et al. (2001)

or Nunez et al. (2010) for their severely obese (BMI $\geq$35 kg/m^2). In contrast some studies did observe significant difference in the knee related or overall physical function reported by patients either pre operatively or post-operatively up to one year or both (Rajgopal et al. 2008; Dowsey et al. 2010). However, a weak but significant negative relation of BMI with follow up knee function at six months and one year after operation and with overall physical health at one year after operation was observed in this study. This result was concurrent with another study which found a significant negative correlation of BMI with one year knee and overall physical function (Stickles et al. 2001), but contrasts with other studies which use regression models with BMI as a predictor variable and find insignificant association of BMI with physical function outcomes (Deshmukh et al. 2001; Escobar et al. 2007; Steven-Lapsley et al. 2010).

Comparison of patient reported outcomes measures with investigator measured or performance measures to assess the effect of obesity within one year after surgery was also done. Poorer KSS knee and function score was seen for obese and morbidly obese at one year (Dowsey et al. 2010) and this was reflected in the greater patient reported difficulty in stair climbing and descending (Stickles et al. 2001). On the other hand, BMI did not have a significant association with timed up and go test, stair climb test and 6 minute walk test as observed by Steven Lapsley et al. (2010). It must be noted that in the latter study (Steven Lapsley et al. 2010) the patient sample was limited up to a BMI of 40 kg/m^2 with no patient in the study having a BMI $\geq$40 kg/m^2. On observing scatter plots of BMI vs. one year OKS/PCS of this study (section 8.1, figs 8.4,8.7), though the negative correlation is significant, it is not very strong and pulled to the poorer side by extreme values with particularly high BMI. This suggests a possibility that particularly poorer outcomes in very high BMI ranges could be pulling the overall outcomes in obese towards the poorer side in the correlation analyses

In conclusion, the improvement in physical function was equal for all BMI groups in this study. While some effect of BMI was seen as a continuous variable, it could be the result of some extreme values in this study which was seen with BMI as high as 49 kg/m^2 with corresponding low outcomes scores. Drawing conclusive evidence with comparison of studies is presently limited with variation among studies with regard to BMI cut off

values used, different outcomes measures used, statistical differences (use of change score or absolute scores or BMI as a continuous variable), control for pre operative scores and difference in study design (matched controls or non matched).

7.2. 6 Is it weight or fat that affects outcome?

From previous evidence in literature, the link between obesity and osteoarthritis has been suggested to be more complex than just a mechanical effect of increased loading of the joint in those with greater body mass. Whether this complexity in the relation between obesity and function is present after the affected joint has been replaced has not been explored. Thus, by defining obesity using five different methods of body composition measurement, this study attempts to explore if mechanical factors and/or other factors associated with obesity play a role in determining the outcome for up to one year after a total knee replacement. The current study results show that none of the body composition measures had any significant group differences for knee specific function and overall physical and mental health related quality of life. But statistically significant associations were observed between BMI, WC and follow up OKS and PCS. However, the association was weak and could be attributed to the outliers in the higher end of BMI/WC. In addition, patients in the higher WHR group felt greater pain during walking six weeks after surgery. Therefore total body mass and trunkal mass by increasing joint loading may have had an effect on pain on weight bearing and physical outcomes and that the level of fat (total body measured by BIA and regional measured by US) did not have any bearing on the outcomes. In order to understand the link between obesity and TKA outcomes, this section discusses the various hypotheses surrounding the nature of association of obesity and the diseased knee joint and the mechanisms by which obesity may or may not affect the outcomes after replacement of the joint as proposed by the current and previous evidence.

There is an obvious link between obesity and the onset of knee osteoarthritis, progression of osteoarthritis and the progression of the condition to a severity requiring a total knee replacement (Felson 1998, Hartz et al. 1986, Strummer et al. 2000, Lohmander et al. 2009, Wang et al. 2009). In order to understand the nature of link between obesity and knee OA, various studies have explored different markers of obesity other than body mass (WC, WHR, body fat, muscle mass) as risk factors for knee OA. While some studies did find a positive association of fat distribution and proportion of fat with knee OA (Abbate et al. 2006, Lohmander et al. 2009, Wang et al. 2009), others did not find a significant association (Hart and Spector 1993, Davis et al. 1990, Hochberg et al. 1995).

The most accepted hypothesis is the mechanical effect of increased loading on the joint obesity has by virtue of increased body mass such that the prolonged overloading of the joint eventually causes cartilage destruction. The association of obesity with non weight bearing joint e.g. joint in the hand (Yusuf et al. 2010, Cicuttini et al. 1996), the fact that all obese have knee OA, gender disparity in the link between obesity and knee osteoarthritis (Felson et al. 1988; Davis et al.1988), stronger association of obesity with knee than other weight bearing joints such as the hip (Wang et al. 2009) point towards a more complex link of obesity on the knee joint rather than just a mechanical effect. Furthermore, there evidence that loss of body fat is more closely associated with symptomatic relief in knee OA than is loss of body weight (Toda et al. 1998).

The definition of osteoarthritis as a joint disorder with cartilage destruction as the main feature has evolved to describe OA as a more systemic disorder which may affect the whole joint including bone, muscles, ligaments and synovium (Pottie et al. 2006). Recent advances in the adipose tissue physiology and the role of leptin in the development of OA has further strengthened the hypothesis that OA is a systemic disease with dysregulation of lipid homeostasis as one of the pathophysiological mechanisms leading to its development (Dumond et al. 2003).

The effect of pre existing obesity on outcomes after TKR has been researched using body mass index as a parameter of obesity. This has been based on the hypothesis of the mechanical effect of obesity such that greater obesity by means of greater body mass will lead to greater loads on the prosthesis and poorer outcomes. The increased risk of

morbidity and mortality due to obesity which is defined as accumulation of body fat has been well documented in literature. Obesity by its effect, metabolic and systemic, puts the patient at a higher risk of surgical complications during operation and afterwards, during the recovery period. These complications during hospital stay and the early post-operative period could in turn affect the rate and level of functional recovery especially in the short term. Because BMI cannot distinguish between fat and lean mass it can overestimate obesity in persons with greater musculature while underestimating obesity in persons with greater body fat for given body weight. Even if these differences in BMI are small, their effects in miscalculation of obesity may have a greater effect when using cut off points to define obesity by BMI. In TKA patients with greater musculature who have a history of high physical activity, BMI though high enough, will not measure obesity because of the high lean mass in the person. Pre operative muscle condition or higher muscle to fat proportion often predicts the post-operative functional ability after TKA (Mizner and Snyder-Mackler 2005). The higher muscle strength in these patients could therefore result in faster recovery in the muscle condition after surgery, lesser strength deficits and early return to activity. On the other hand patients with a lower BMI but higher fat in proportion to the body mass (for e.g. in women), would have less peripheral muscular support. Also higher chances of lower activity in the latter group would lessen the physiological stimulation for joint recovery and consequently, the benefit of a near normal joint mechanism. However, in this study, body fat (as total body fat percentage and regional fat thickness), distribution of trunkal mass in addition to BMI did not show an effect on the patient perceived knee and overall health. The statistically significant but weak association of higher BMI and WC with follow up knee and physical health outcomes and the trend of greater pain during weight bearing activities in patients with higher WHR six weeks after surgery would seem to indicate that these measures could have some influence on the physical outcomes. From this it can be speculated that total body mass and trunkal mass could by means of increased loading on the replaced joint affect function to some extent irrespective of muscle/fat proportion. However, future appropriately powered studies will need to be carried to confirm this.

Our results obtained from BMI as a measure of obesity is consistent with other studies assessing patient perceived outcomes for up to one year after surgery, as has been

discussed in the previous section. Some deficits in function however were seen in obese by Stickles et al. 2001; Naylor et al. 2008; Dowsey et al. 2010, but these authors conclude that while there are some deficits in function in obese, the patient perceived benefit are high enough for obesity to not be a contraindication to surgery. While some of these studies did see a poorer function measured by lower function score in obese, the improvement in function was in obese was at par with the non-obese. Some of the poor function was seen in the form of poorer function score of KSS and difficulty during stair climbing and descending and increased use of walking aids (Stickles et al. 2001; Dowsey et al. 2010). The function score of KSS consists of patient answered questions regarding stair climbing, walking and use of walking aids. Peak forces at the knee during activities like stair climbing and descending are as high as 7-8 times body weight (Griffin et al. 1998) and it is hypothesized that in activities involving higher joint forces a higher body mass will further add to the forces to reach a threshold inducing pain and difficulty performing these activities due to the greater muscular strength required. This hypothesis is supported by also by longer term studies assessing function by KSS scoring, Foran et al. (2004b) with a follow up of seven years, Jackson et al. (2009), follow up of nine years; Griffin et al. (1998), follow up of ten years; Foran et al. (2004a), follow up of 15 years. However other study results which do not support this hypothesis see no difference in KSS scores between obese and non-obese at five years (Amin et al. 2006; Dewan et al. 2010) or at ten years (Spicer et al. 2001) and therefore suggestive of the alternative to the above hypotheses that the added body mass does not increase the load on the joint enough to reach the threshold for pain and discomfort or that if the load on the joint may be greater in the obese, the lower physical activity levels in the obese (McClung et al. 2000) may compensate the increased load on the joint. Consistently poorer results in morbidly obese seen in studies assessing morbidly obese with non-obese (Winiarsky et al. 1998; Amin et al. 2006; Krushell and Fingeroth 2007) has lead to these studies suggesting that perhaps the much higher body mass in this patient groups may not be compensated by lower activity levels. However, it must be noted that as opposed to McClung et al. (2000), Foran et al. (2004a) and Dewan et al. (2010) did not see lower physical activity levels in their obese groups.

Laboratory studies have shown increased wear and tear in polyethylene on metal prosthetic models with greater loads (Barbour et al., 1995; McKellop et al. 1995). Furthermore, the higher implant failure rates at long term in obese seen by Foran et al. (2004a) and Vasquez Vela Johnson et al. (2003). A review by Gillespie and Porteous (2007) suggests that laboratory findings may be equally relevant in a clinical setting where active and heavier patients compromise the longevity of the prosthetic implant.

Despite the varied results for the effect of obesity on outcomes following TKA, majority of the studies conclude that the patients perceived benefits of pain relief and satisfaction obtained from the surgery is substantial. Even studies which did find poorer results in obese in some aspects of functional recovery acknowledge that the pain relief and satisfaction from surgery are substantial enough for obese to be equally eligible for TKA as non-obese. The current study measured different aspects of obesity including body fat, regional fat and fat distribution as obesity is not just a function of body mass and height and is associated with different metabolic and behavioral affection which may influence outcomes. The complication rates after the surgery and pre operative mental health of the patients in our study was not different between obese or non-obese and did not cause any difference in the overall outcomes between obese and non-obese. Using the standard cut off values of BMI and median split values for other measures (WC, WHR, BIA, US) to divide the patients into groups also showed no effect of obesity on the outcomes.

7.2.7 Section Summary

This section explains the results obtained from the study and how it fits with the rationale behind assessment of body composition (WC, WHR, BIA, US) in addition to BMI to assess the effect of obesity and the various hypotheses behind any or no effect of obesity. This study is innovative in assessing influence of body composition (WC, WHR, BIA, US and BMI) on outcomes following TKA.

The alternate hypothesis that a higher level of obesity (higher BMI, WC, WHR, body fat percentage and regional fat thickness) will result in a poorer function outcome, poorer quality of life and higher levels of pain was rejected. The null hypothesis of this study; that obesity did not result in a poorer function outcome, poorer quality of life and higher levels of pain was accepted.

However, the current study is underpowered as it was not able to detect statistically significant differences in measures which showed good effect sizes (Cohen's $d > 0.5$) between body composition groups (WC, WHR, BIA, US and BMI). The study is especially low in participant number of morbidly obese patients thus not allowing for separate analysis. A negative correlation between BMI and WC and physical function levels at follow up was found but this was observed due to some extreme values at the higher end of the BMI/WC. A significantly greater level of pain during walking six weeks after surgery was observed for patients in the higher WHR group and a higher levels of pain in patients belonging to the higher WHR groups during stair climbing was also observed, though not statistically significant (Cohen's $d > 0.5$). No difference in the knee and overall health outcomes was found between obese and non-obese groups defined by any of the five body composition methods (WC, WHR, BIA, US and BMI) even after controlling for pre operative self-report function. This lack of effect on knee and overall health outcomes seen in the current study and previous studies suggests that as far as patient perceived benefits are concerned obesity (measured by WC, WHR, BIA, US and BMI) has little or no impact at short term (up to one year).

CHAPTER 8: GENERAL DISCUSSION

8.1. Chapter overview

This chapter presents the key finding of the thesis including the literature review, retrospective study, reliability tests for body composition measures and the prospective study. Comparison of the findings of the retrospective and prospective studies is then done to derive conclusions about the effect of BMI on patient reported outcomes after TKA. This is followed by a section integrating the key discussion points of the three chapters (literature review, retrospective study and the prospective study) to derive meaningful conclusions regarding the effect of obesity (measured by WC, WHR, BIA, US and BMI) on patient reported outcomes following. Strength and limitations of the studies are then discussed followed by the implications of the findings on clinical practice. Finally, recommendations have been made for future research.

8.2. Key findings

The key findings of the thesis are as summarized and presented in Table 32.

Table 32 Key findings of the thesis

Literature review	• Inconsistencies in the evidence, making it difficult to identify if an effect of obesity (BMI) on outcomes after TKA exists conclusively. These inconsistencies seem to arise primarily as a result of the differences between the studies with respect to classification of obesity based on BMI, differences in measurement of outcomes, differences in the baseline characteristics of the patients and length of follow up. • Inconsistent evidence of lower complication rates and poorer functional outcomes across BMI classification of $\geq$30 kg/m^2. • More consistent evidence of higher complication rates across BMI classification of $\geq$35 kg/m^2. • More consistent evidence of higher complication rates and poorer functional outcomes across BMI classification of$\geq$40 kg/m^2 (when compared with BMI <30 kg/m^2). • Studies with longer follow up indicated poor physical function in patients with BMI $\geq$ 30 kg/m^2. • In studies finding an effect, stair climbing, stair descending and walking was found to be more difficult in obese (BMI$\geq$30 kg/m^2)
Retrospective study (Chapter5)	• Overall physical health at one year after TKA worsens with increasing pre operative BMI (correlation analysis) • Knee function (OKS) and overall physical and mental health and complication rates are unaffected by pre operative BMI grouping (using BMI $\geq$ 30kg/m^2 as cut-off)
Reliability study	• Excellent repeatability (intra-rater) of assessment of body fat percentage by bioelectrical impedance analysis. • Excellent reliability observed for both inter-rater and intra-rater measurements of fat thickness above knee using ultrasonography.

Prospective study (Chapter 7)	• Overall physical health (PCS) at one year after TKA worsens with increasing pre operative BMI (correlation analysis). • Overall physical health (PCS) at six months after TKA worsens with increasing pre operative waist circumference (correlation analysis). • Overall mental health (MCS) at six months after TKA worsens with increasing pre operative waist to hip ratio (correlation analysis). • Knee function (OKS) worsens at six months and one year after TKA as pre operative BMI, waist circumference increase (correlation analysis) • Knee function, overall physical and mental health were unaffected by grouping using WHO definitions and median split technique according to pre operative classification of BMI waist circumference, waist to hip ratio, body fat percentage and fat thickness. • Patients with a higher waist to hip ratio experienced greater pain than those with pre operative waist to hip ratio ≤ 0.95 during walking six weeks after TKA.

8.3. Comparison of retrospective study and prospective study results

8.3.1. Patient baseline characteristics

The distribution of baseline characteristics and comorbidity across BMI groups were similar in both studies except for a higher proportion of females and hypertensive patients in the obese group in the retrospective study sample. Both studies had a significantly higher number of type II diabetes patients in their obese group (BMI $\geq$ 30kg/m^2). The average age of the sample in the prospective study was higher than that of the retrospective study (70.6 years vs. 66.7 years).

Mean, standard deviation, Cohen's effect sizes and p values for outcome measures for both studies are shown in Table 33.

For both studies the baseline knee function (baseline OKS) was poorer in obese. The difference between means of obese and non-obese for the retrospective study was 3.5 and that for prospective sample was 2.8, however, only the difference in the retrospective sample reached a statistical significance (p = 0.003) even though the effect size was higher for the prospective study (0.4 and 0.48), probably due to lower sample size in the

8.1.8. Effect of body composition: Between group comparison

prospective study which did not have sufficient power to detect a significant difference.

Noting the differences in baseline and follow-up between the two studies, the retrospective study which is probably more representative of the TKA population has lower baseline and follow-up values while patients who consented for the prospective study had better function and health

Table 33 Mean and standard deviation (SD), Cohen's effect size (d) and p-value for between group differences for the retrospective and prospective study

	Retrospective study					Prospective study				
		Obese	Non-obese				Obese	Non-obese		
	N	Mean (SD)	Mean (SD)	ES	p-value	N	Mean (SD)	Mean (SD)	ES	p-value
OKS1	45vs. 31	16.7 (7)	19.6 (8)	-0.4	0.003	38 vs.23	20 (5.9)	22.9 (6.5)	-0.48	0.082
OKS2	45vs. 31	32.6 (8.7)	31.7 (10.2)	0.09	0.711	28 vs.17	35.3 (10.9)	38.11 (7.7)	-0.30	0.89
OKS3	45vs. 31	33.6 (9.2)	33.7 (10.9)	-0.01	0.664	18 vs.14	39.2 (7.9)	40.9 (5.9)	-0.25	0.77
PCS1	45vs.36	30.3 (7.4)	30.4 (7.2)	-0.01	0.902	38 vs.23	30.9 (6.6)	32 (8.5)	-0.15	0.573
PCS2	45vs.36	37.1 (10)	38.3 (10)	-0.12	0.581	29vs.19	44.4 (15.4)	46.8 (16)	-0.16	0.95
PCS3	45vs.36	36.8 (9.7)	41.3 (11.1)	-0.44	0.091	18 vs.14	44.8 (10.6)	46.1 (7.7)	-0.14	0.82
MCS1	45vs.36	49.2 (10.8)	50.9 (12.1)	-0.15	0.364	38 vs.23	50.7 (12.7)	52.7 (10.8)	-0.17	0.498
MCS2	45vs.36	52 (10.5)	51.5 (10.6)	0.05	0.805	29 vs.19	53.7 (12.9)	57.8 (12.7)	-0.33	0.171
MCS3	45vs.36	51.9 (9.4)	51.7 (9.9)	0.02	0.827	18 vs.14	55.8 (6.7)	52.5 (11.3)	-0.38	0.676

OKS1: OKS at baseline, **OKS2**: OKS at six months follow up, **OKS3**: OKS at one year follow up

PCS1: SF-12 physical component summary at baseline, **PCS2**: SF-12 physical component summary at six months follow up, **PCS3**: SF-12 physical component summary at one year follow up

MCS1: SF-12 mental component summary at baseline, **MCS2**: SF-12 mental component summary at six months follow up, **MCS3**: SF-12 mental component summary at one year follow up

8.3.2. Group differences across BMI ≥ 30 kg/m^2

Despite the differences in the baseline data, no group differences were found at six month or one year follow up (retrospective study) and at six weeks, six months and one year follow up (prospective study) Although no difference were found between obesity groups, the thesis findings do reveal a weak negative association of body mass index and waist circumference with patients perception of knee specific function (prospective study) and overall physical health (both prospective and retrospective studies). using absolute scores. Thus even with poorer knee function pre-operatively (retrospective study), the post-operative scores were not significantly different between groups. Even after controlling for baseline scores using change scores or ANCOVA in the studies, no differences were found between the BMI groups.

8.3.3. Correlation Analysis

Negative correlations between BMI and OKS i.e., worse knee function with increasing BMI, at six months ($r = -0.337$, $p = 0.024$) and one year ($r = -0.416$, $p = 0.018$) were stronger and statistically significant in the prospective study sample and not in the retrospective study sample (six months $r = -0.039$, $p = 0.737$ and one year $r = -0.103$, $p = 0.376$). However, both studies revealed significant association of BMI and physical component of SF-12 health survey i.e., worse overall physical health as BMI increased.

The findings of the two studies reveal that in the thesis patient samples, a BMI cut off value of $\geq$ 30 kg/m^2 does not indicate a poorer outcome. However, both studies detected some effect of BMI on the overall physical health when using BMI as a continuous variable. The lack of between group differences for overall physical health across a BMI of 30 kg/m^2 in both studies was reflected in the lack of an obvious relationship between BMI of 25 and 35 kg/m^2 in the scatter plots. But the scatter plots for these studies show several cases with the lowest (poorest) scores at the higher end of the BMI. Comorbidity which were which were significantly higher in the obese such as type II diabetes (both

studies) and hypertension (retrospective study) could have impacted the overall physical health of the higher BMI patients.

The two studies however differed in detecting an effect of BMI on knee function by OKS. The scatter plots of the significant correlations for the prospective study studies show values scattered largely between BMI of 25 and 35 kg/m^{2}with no obvious negative relation (Figure 10-16, Chapter 7) but a few cases with very low (poor) OKS scores and higher BMI. On comparing these scatter plots with that the BMI vs. OKS scatter plots with the retrospective data, it was observed that while low scores were also present in the retrospective sample, they were scattered between lower and higher BMI and were further away from the regression line. Moreover, the larger sample size in the retrospective study would make the correlation analysis less sensitive to extreme values.

8.4. The influence of obesity measures on outcomes following TKA

8.4.1. Classification using BMI ≥ 30 kg/m^2

From the current evidence and that from previous studies it can be concluded that defining obesity with a BMI cut off level of greater than or less than 30 kg/m^2 is not definitive in detecting an effect on patient reported outcomes or complication rates within one year after TKA. This is also reflected in the scatter plots of BMI vs. outcomes in the current thesis, with outcomes widely spread across this cut off value indicating no clear relationship between the variables ranging from a BMI value of 25 -35 kg/m^2. Inconsistencies in evidence also exists for longer follow up periods ranging from five to ten years suggesting that this cut off value of BMI is also not definitive in predicting an effect of obesity beyond one year following TKA. Beyond ten years after TKA, this classification does seem to predict a poor function in obese.

8.4.2. Classification using BMI ≥ 35 kg/m^2

Higher and more severe complication rates have been observed for patients with BMI ≥ 35 kg/m^2, however, patients perceived function was not different across groups based on this classification (Chapter 4). Correlation analysis of significant relations in the thesis (Chapter 5 and Chapter 7) indicated that while the relation between BMI and outcomes was not clear between the BMI range of 25 -35 kg/m^2, beyond this range the negative relationship appeared more clearly such that the scatter plots of BMI and outcomes in the current thesis showed some decreasing (worsening) of outcome score after BMI of 35 kg/m^2, but due to the limited number of patients in the study (and therefore also a lack of group analysis across this BMI value) it is not possible to draw conclusions.

8.4.3. Classification using BMI ≥ 40 kg/m^2

Consistency in the previous evidence of poorer outcomes in patients with a BMI greater than 40 kg/m^{2}and a clearer negative relation for these higher but few BMI values and functional outcomes in the current evidence can suggest more conclusively that patients at such high BMI level are at a higher risk of poorer outcomes. However due to few cases which could be classified as morbidly obese in the studies of the current thesis, if group differences between BMI ≥ 40 kg/m^{2}and BMI ≤30kg/m^2 as seen by previous study exist could not be assessed in the current thesis. Also, if a risk of poorer outcomes extends to patients in the BMI range of 35 – 40 kg/m^2 is unclear from the current evidence.

Therefore while a BMI greater than 30 kg/m^{2}does not indicate a poor outcome, an effect of BMI cannot be completely negated as high values of BMI do seem to be associated with poorer outcomes. A specific value of these higher BMI after which a poorer outcomes can be expected is cannot be given from the current evidence because of the limited number of patients in the studies.

8.4.4. Body composition and outcomes

Measuring obesity as body fat percentage or regional fat did not detect an effect of obesity (Chapter 7). Therefore the effect of obesity on outcomes by the association of body fat percentage with morbidity risk and association of a possible effect of regional fat thickness on morbidity, leg muscle/fat proportion and complication during recovery due to intra-operative difficulties was not detected. This suggests that there is no negative effect of obesity (BIA and US) on outcomes after TKA through these associations of body composition. However, anthropometric measure of waist circumference and waist to hip ratio were able to detect some effect of obesity on knee function.

The negative association of BMI and waist circumference with knee function at follow up suggests role of body mass and upper body mass in the higher ranges on knee function (Chapter 7). There is also some previous evidence of a negative association of BMI with weight bearing activities including walking, stair climbing and descending at one year following TKA and also after (Chapter 4). Oxford knee scores and PCS of SF-12 have question related to the patient perceived difficulty with weight bearing activities such as stair climbing and walking and it is known that during these weight bearing activities, peak stresses on the joint are high. Therefore, an effect of increased mass by additional stress on the joint during these activities could be possible such that a greater total body mass and/or trunk mass by increasing the mechanical load on the joint could result in producing stresses over the joint which reach a threshold to cause pain. Moreover, differences between WHR groups for pain during weight bearing activities of walking, stairs climbing and descending six weeks after surgery (effect sizes of 0.59, 0.64 and 0.36) suggest that android distribution of obesity can lead to greater pain during weight bearing activities after TKA. These findings suggest an impact of obesity in terms body mass and/or upper body mass during on weight bearing activities.

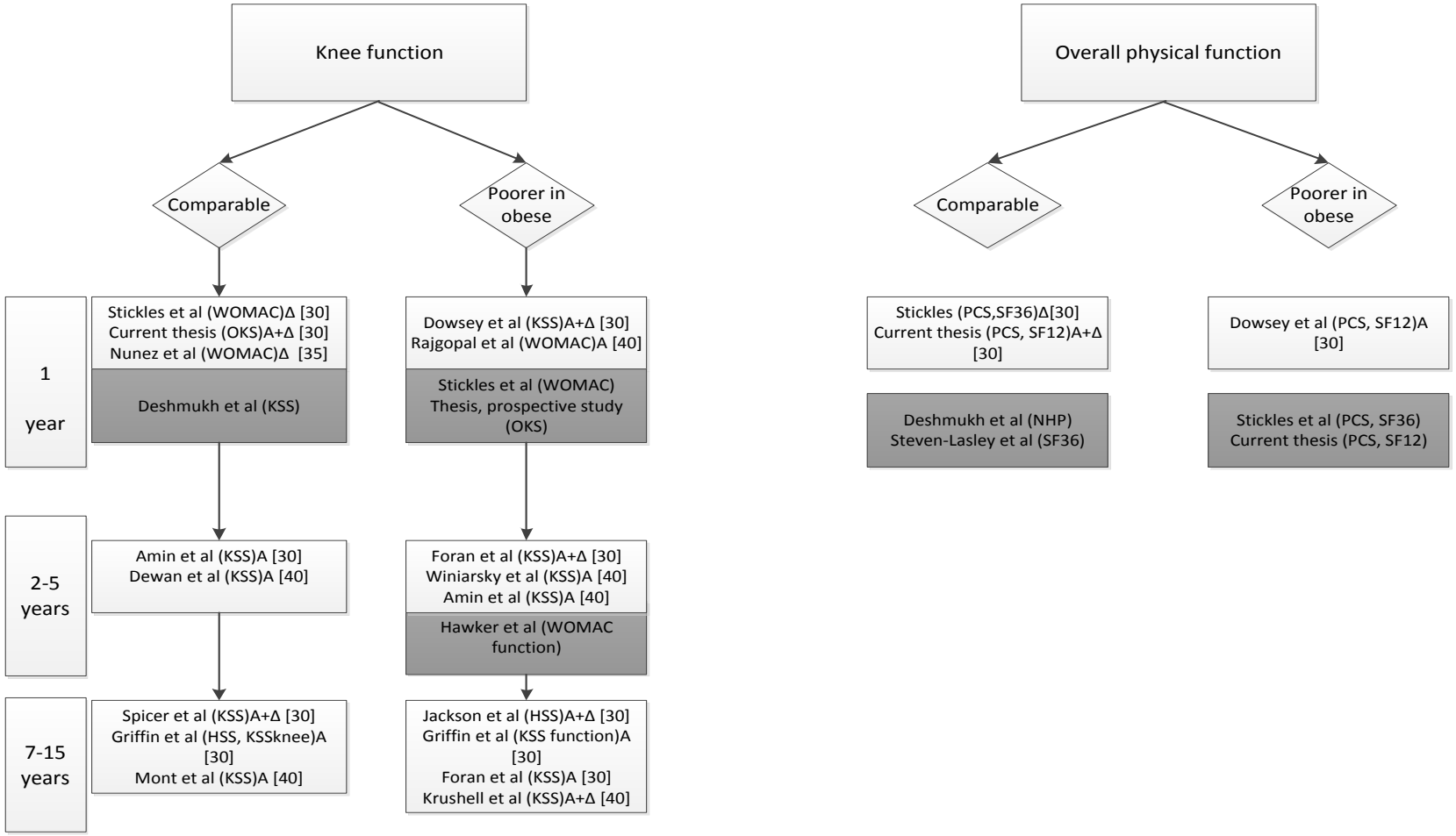
Negative relationships between waist circumference and six months PCS and waist to hip ratio and MCS of SF-12 at six months was seen in the prospective study though significant, were very weak and due to two cases with very high PCS/MCS values of 99 on the lower waist circumference/waist to hip ratio group pulling the relationship towards

a significant level and therefore no meaningful conclusion. This again reflects the limitation of the study with respect to a small sample size.

As discussed earlier in the thesis (Chapter 3 and Chapter 7), the association of obesity with the joint is complex and mechanism by which it can have a negative effect on the joint is unclear. Obesity, in addition being a function of body mass relative to height is also associated metabolic and behavioral patterns which could result in poor function. However, obesity parameters other than body mass in this thesis (which were body fat percentage and regional fat thickness) could not identify any negative outcomes for obese. The lack of differences between groups on analyses of obesity using BMI classification of obesity indicates that the cut off value of 30 kg/m^2 though universally accepted as indicative for health risks associated with obesity, this cut off value is not indicative of good or poorer outcomes following TKA. Groups based on waist circumference, waist to hip ratio, percentage body fat and regional fat thickness in addition to BMI were also not indicative of good or poorer outcomes following TKA.

Fig. 16 shows a flow diagram representing the evidence from the current thesis and previous studies on the effects of BMI on outcomes after TKA.

Flow diagram summarizing the possible effects of obesity gathered from literature is shown in Figure 17.



BMI cut off values for classification are indicated in the square brackets. A: Absolute score, Δ: change score. Areas shaded in grey represent analyses with BMI as a continuous variable.

Figure 16 Flowchart representing the evidence on the effect of BMI on knee specific and overall physical function outcome

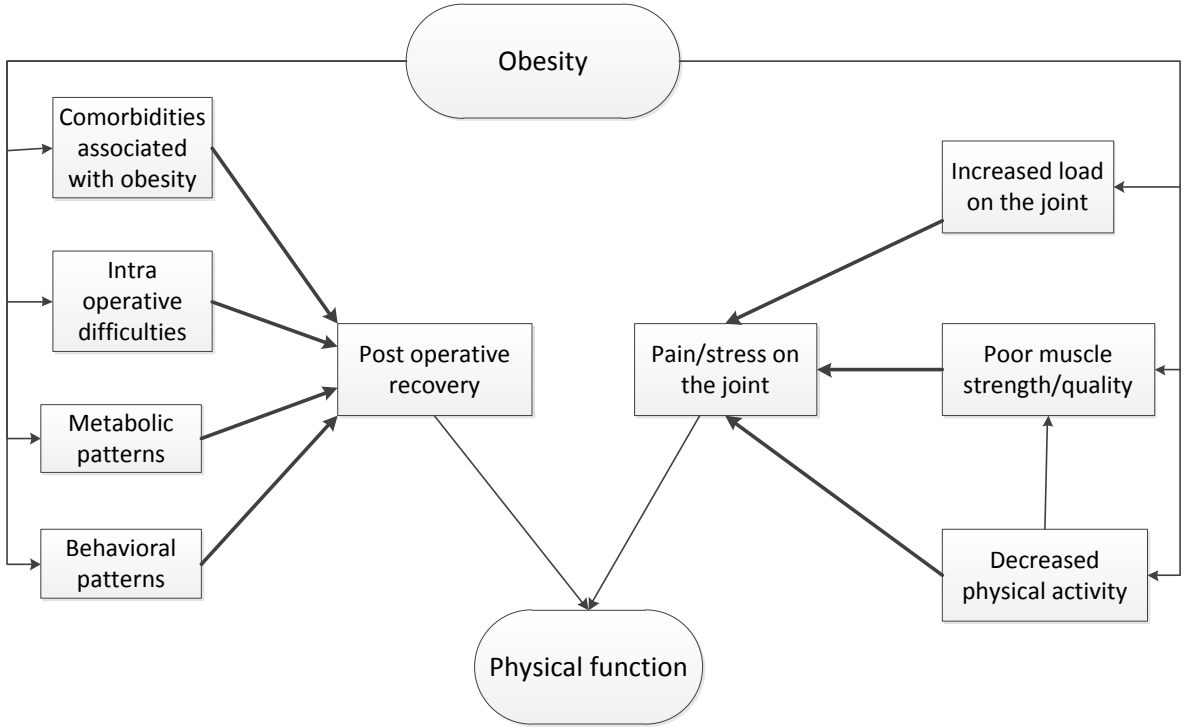


Figure 17 Possible effects of obesity on physical function after TKA

8.5. Strengths and limitations of the study

8.5.1. Strengths

The effect of obesity (assessed by BMI) on TKA outcomes has been researched in prospective studies, retrospective studies, case control studies. Considering the inconsistent findings of the effect of BMI on outcomes following TKA from the literature review and the retrospective study of the thesis and the previously discussed limitations of BMI as a method of measuring obesity, the prospective study of the thesis is the first to assess the influence of different markers of obesity (waist circumference, waist to hip ratio, BIA and ultrasonography) in addition to BMI on the outcomes following TKA. The findings of the thesis thus provide an in depth evaluation of the effects of obesity on outcomes following TKA.

The chosen body composition methods in this thesis (waist circumference, waist to hip ratio, BIA, ultrasonography and BMI) are clinically viable methods which assess different aspects of obesity allowing an exploration of the effects of true obesity on the outcomes after TKA.

Attempts were made to maintain sample homogeneity with recruitment of patients undergoing surgery at a single institution (for both studies), under a single surgeon (retrospective study) with identical post-operative care.

Previous research in the area have mostly used one method of evaluation, either as group differences between BMI groups or BMI as continuous data. The research question of whether obesity affects outcomes following TKA has been addressed in this thesis employing both an exploratory (correlations) and group comparison method. This has been done by using body composition measurements (waist circumference, waist to hip ratio, BIA, ultrasonography and BMI) as continuous variables as well as using the

standardized cut off values of BMI and median values for other methods to divide participants into obese and non obese groups.

8.5.2. Limitations

Study design

When compared to randomized controlled trials, prospective and retrospective cohorts include a broader range of patients and thus deemed more representative of clinical practice (Ligthelm et al. 2007). However, because of non randomized nature, observational studies have an increased likelihood of bias (Grimes and Schulz 2002, Thadhani and Tonelli 2006). For example, from the differences in the values of the mean score between the prospective and the retrospective studies it is clear that patients who participate in the prospective study have better health and knee function compared as opposed to the retrospective study where patients were not active participants and data was derived from hospital records. This could be suggestive of a more representative sample in retrospective compared to the prospective study.

Participant recruitment was done from a single institution for both studies and from the patients list of a single surgeon for the retrospective study to allow for some homogeneity in the sample however, this also worked to limit the number of participants available for assessment within the given time frame and also limits the generalizability of the results.

Like previous studies, the research question for the current thesis addresses the effect of pre operative obesity status on the outcomes after surgery and therefore involved the assessment of obesity pre operatively which was not followed up post operatively. Previous studies have reported weight gain after TKA (discussed in section 4.6.2, chapter 4) and lack of post operative body composition data does not allow evaluation of any change in any of the body composition markers and if an interaction exists between post operative or change in body composition and outcomes in this thesis.

The section of the thesis addressing the practical considerations for measurement of body composition (section 7.2.3, chapter 7) highlights the difficulty in maintaining the

standardized hydration conditions for BIA and while assessment times were adjusted to accommodate participant convenience and participants were reminded of the conditions to follow prior to the assessment, if adequate hydration condition was maintained for all participants cannot be ascertained. More accurate methods of measurement of body composition (described in section 3.5) which could measure body composition more accurately and in more detail were not used due to safety (radiation exposure) and feasibility issues.

The thesis aimed to assess self report outcomes to evaluate the patient's perception of their outcome which is an important determinant of the success or failure of an elective procedure. Therefore measurement of patient physical performance, objective assessments such as measurement of muscle strength and range of motion or a combination of outcomes have not been employed in the two studies and limit the studies in the evaluation of an objective or a 'technical' outcome of TKA.

The prospective study was not powered to detect a statistically significant difference between the WHR groups for pain while stair climbing. This difference had an effect size of 0.64. Moreover, the difference of 1.6 points on the VAS scale may be also regarded a clinically significant. To detect an effect size of 0.64 in this outcome, appropriately powered studies should have at least 39 patients in each group to achieve a power of 80% at 5% level of significance. The limited number of participants; especially at follow up the studies in this thesis render it underpowered. Meaningful statistical analysis of the morbidly obese group separately was also not possible with very few numbers of morbidly obese patients in the retrospective study (n = 19) and prospective study (n = 4).

Confounding

Confounding is an issue of alternative explanation to the effect on outcome. While standard midline incision is used for all standard TKA procedures, the type of prosthesis varied. The samples in the two studies were also not restricted to patients with a primary diagnosis of OA with a few rheumatoid arthritis patients in both studies (11 in retrospective study and 4 in the prospective study).

Possible influence of the pre-operative score on the post-operative score was controlled in both studies using ANCOVA in the prospective study and analysis of change score in addition to absolute score in the retrospective study.

Measurement of the impact of other possible confounding factors such as physical activity levels, weight change after surgery, effect of contralateral and other joint disease and personal factors affecting recovery that have been discussed in the previous section (section 4.6, chapter 4) were not recorded in this PhD.

Age group (mean 70.6 ± 8) in the study reflects the national average age of those undergoing primary TKA reported in Scottish Arthroplasty Register report for the year 2009. According to the national trend, a larger proportion (approximately 60%) of primary TKA patients is female. The prospective study had a slightly lower percentage of females (54%) in the sample and thus a more equitable distribution of gender. While the literature is not consistent with effect of age and gender on outcomes, there is some evidence that older age is associated with worse self-report function particularly in women (Santaguida et al. 2008, Cushnaghan et al. 2008). Lack of an adequate sample size did not allow for age or gender to be used as a covariate in the studies to control for the influence of these factors.

The number of obese was larger than non-obese in the studies reflecting the finding that population of obese in TKA population is high (Fehring et al. 2007). The disparity in numbers between BMI groups was not too high to not allow meaningful analysis. When grouping was done according to previously used classification of waist circumference, waist to hip ratio and body fat percentage, a very high proportion of patients were in the 'obese' group and the difference between the group numbers was too high for any meaningful statistical analysis and thus we used a median split techniques for these measures. Previously used classifications of these measures would be possible with a larger sample size.

If more severe comorbidity observed in a few cases of high BMI range (BMI >40 kg/m^2) had an effect on the outcomes was difficult to judge from the studies which further

highlights the limitation of our study in lacking a separate analysis of the morbidly obese groups.

Bias: Response to follow up

For the prospective study, while the six week outcomes had a high response rate, the drop- out rates were high for six month and one year follow up (29.7 % dropout & 50 % dropout respectively). This loss to follow up can be a limiting factor resulting in a response bias as patients who do not response to health questionnaire are often those who have a poorer function outcome (Kim et al. 2004). Moreover, the pain sores were not available for any patient at six month or one year as these are not collected for the hospital database. Since pain may improve even after one year following surgery, follow up pain measurement at six weeks at best can offer an estimate of the rate of recovery from pain and not really the comparison of improvement in pain.

Pain relief is heavily dependent on the patient's use of pain medication and while the prescription of pain medication is standard at the time of discharge, the consumption is controlled by the patient. This study like others did not record pain medication.

8.6. Implications for practice

The current thesis questions the method of defining obesity for total knee replacement patients in clinical practice and research. The findings of the thesis show that categorizing patients as obese using a BMI cut off of 30 kg/m2 does not reveal a poorer outcomes with respect to post-operative complications, level of knee function and overall physical and mental health and pain in the early post-operative period. no difference between groups were found either on using other body composition methods which are closely related to morbidity in addition to BMI in the latter study of the thesis. The obesity categories for these body composition measures in the thesis were based on a median split and whether

known classifications for some of these measures (waist circumference, waist to hip ratio, body fat percentage) based on morbidity risk would find a difference in outcomes is not known from this thesis. Although no difference were found between obesity groups, the thesis findings do reveal a weak negative association of body mass index and waist circumference with patients perception of knee specific function (prospective study) and overall physical health (both prospective and retrospective studies). Another finding of the thesis was that patients with higher (greater than 0.95) waist to hip ratio indicated greater pain on weight bearing activities (walking and stair climbing) in the early post-operative period.

The obese patients (according to BMI) in the thesis samples had higher proportions of hypertension and diabetes which could have impacted the relation between obesity and overall physical function and thus indicative of an effect of obesity on function through a metabolic pattern. The lack of group difference but a negative association with physical function outcome using continuous variables in this thesis suggests that while outcomes are similar across a cut-off point of 30 kg/m^2, higher BMI through a variety of mechanisms affect outcomes at short term. Although at what value of BMI or other body composition measures outcomes begin to be affected cannot be known through the results of the thesis. Moreover, since obese patients perspective of function improved as substantially from the per operative to post-operative stage as that in non-obese, TKA is an effective procedure for irrespective of obesity, rationing of TKA on the basis of BMI alone is not justified. However, keeping in mind the level of obesity and the associated comorbidity in the individual patients; carefully considered medical counseling, encouragement to lose weight, preferably as early as possible during the course of the disease and medical or surgical interventions for highly obese patients would be recommended in clinical practice.

8.7. Future research recommendations

The current thesis (prospective study) is the first to explore the effect different definitions of obesity on outcomes following TKA. Both studies in the thesis did not see striking effect of obesity on the self-report outcomes; however, the studies were restricted in their sample sizes therefore not adequately powered to demonstrate the influence of body composition on TKA outcomes. This study can be considered as a pilot based on which future studies on body composition and TKA outcomes can be developed. Particularly, analysis which includes a larger number of morbidly obese patients is important as the correlation analysis in this study and previous gives suggests poor outcomes in highly obese patients. A larger sample size would also allow for inclusion of confounding factors discussed in the earlier sections as covariates in analyses.

The current study has defined obesity in different ways other than just a state of increased body mass. The measures used in the study have been chosen such that their applicability in a in a clinical setting is practical and feasible. There are several options for defining obesity which can be used by future studies and though there is not a 'gold standard' method more accurate methods for determining fat mass that that used in this study such as DEXA scans can be added for more accurately defining adipose levels in future research. Also, in future studies with larger samples it would be feasible to group patients using these body composition measures according to classifications based on morbidity risk instead of median split technique to identify if there is a difference in outcomes.

Patient perception of the benefits of the surgery is important in assessing the success of an elective procedure and the current study has focused on the effect on patient reported outcome measure. Woolhead et al. (2005) in a qualitative study identified that patients expression of outcomes through formal questioning similar to that when using questionnaires indicates a keenness of the patients to state that the outcomes of their TKA was good. But when given time to describe their outcomes patients acknowledged continued problems with pain and mobility and tried to rationalize these continued difficulties and tend to take responsibility for them. It is also recognized that patient

perceived outcomes after arthroplasty is not always congruent with that of a health care professional (Leiberman et al.1996). Like most studies, the use of the chosen outcomes measures in this study does not address these complex issues surrounding the improvement after surgery. A large scope of outcomes definitions and measurements which could be used in combination is available for future research assessing effect of body composition.

CHAPTER 9: THESIS CONCLUSION

The literature review of the effect of BMI on TKA outcomes revealed inconsistencies in the evidence due the differences classification of obesity based on BMI, differences in measurement of outcomes, differences in the baseline characteristics of the patients and length of follow up in previous studies. Conflicting results appear primarily among studies assessing an effect of BMI on outcomes using a BMI classification of BMI > 30 kg/m2 with many studies not finding a difference across this BMI value. Both the retrospective study and the prospective study reveal no group differences and no definitive negative association between the BMI ranges of 25-35 kg/m2. These studies thus give evidence that group division of obesity based on the WHO classification of greater than or less than 30 kg/m^2 cannot identify an effect of obesity on outcomes. More consistent results in pervious evidence is seen for the morbidly obese group with a BMI cut off of > 40 kg/m2. Also the negative association seen with BMI as a continuous variable on physical function is clearer only at higher BMI ranges, could indicate an effect in the higher ranges of BMI.

Body composition measures of body fat percentage and regional fat thickness did not find any effect of obesity on outcomes in this thesis. Waist circumference and waist to hip ratio (only pain during walking after TKA) did find some effect of obesity similar that that found by BMI. From this thesis, it can be concluded that anthropometric measures of BMI and waist circumference and to some extent waist to hip ratio are best to determine any effect of obesity.

Due to the limited number of participants, at which high value of BMI a definite negative outcome can be seen, cannot be derived from the results of this thesis. The limited number of participants in both studies of the thesis renders it underpowered and adequately powered future studies could give more definitive answers to the effect of body composition on outcomes following TKA.

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APPENDIX

Appendix A: Retrospective Study Normality Tests

Table A1: Normality Test for OKS Absolute scores

BMI group of the patient		Shapiro-Wilk		
		Statistic	df	Sig.
OKS pre using new scoring	non obese BMI < 30	.976	31	.691
	obese BMI ≥ 30	.965	45	.184
OKS 6mo new scoring	non obese BMI < 30	.951	31	.168
	obese BMI ≥ 30	.920	45	.004
OKS 1year new scoring	non obese BMI < 30	.913	31	.015
	obese BMI ≥ 30	.907	45	.002

Table A2: Normality Test for OKS Change scores

BMI group of the patient		Shapiro-Wilk		
		Statistic	df	Sig.
oks 6 mo - oks pre	non obese BMI < 30	.978	31	.767
	obese BMI ≥ 30	.982	45	.712
oks 1 yr - oks pre	non obese BMI < 30	.971	31	.536
	obese BMI ≥ 30	.977	45	.490

Table A3: Normality Test for PCS (SF12) Absolute and Change scores

BMI group of the patient		Shapiro-Wilk		
		Statistic	Df	Sig.
pre operative physical component sf12	non obese BMI < 30	.896	36	.003
	obese BMI ≥ 30	.984	45	.793
post operative physical component sf12	non obese BMI < 30	.944	36	.066
	obese BMI ≥ 30	.963	45	.153
follow up physical component sf12	non obese BMI < 30	.918	36	.011
	obese BMI ≥ 30	.968	45	.236
pcs 6mo - pre	non obese BMI < 30	.957	36	.169
	obese BMI ≥ 30	.971	45	.312
pcs 1 yr - pre	non obese BMI < 30	.953	36	.133
	obese BMI ≥ 30	.974	45	.400

Table A4: Normality Test for MCS (SF12) Absolute and Change scores

BMI group of the patient		Shapiro-Wilk		
		Statistic	Df	Sig.
pre operative mental component score of SF12	non obese BMI < 30	.915	36	.009
	obese BMI ≥ 30	.907	45	.002
post operative mental component score of SF12	non obese BMI < 30	.874	36	.001
	obese BMI ≥ 30	.876	45	.000
follow up mental component score of SF12	non obese BMI < 30	.868	36	.001
	obese BMI ≥ 30	.953	45	.066
mcs 6 mo - pre	non obese BMI < 30	.961	36	.225
	obese BMI ≥ 30	.964	45	.172
mcs 1 year - pre	non obese BMI < 30	.959	36	.198
	obese BMI ≥ 30	.960	45	.123

Appendix B: Prospective Study Normality Tests

Table A1: Normality test for all follow up data (prospective)

Outcome measure	Shapiro-Wilk Normality test		
	Test statistic	df	Significance
OKS pre op	0.98	61	.305
OKS 6 weeks	0.97	61	.217
OKS 6 months	0.89	45	.000
OKS 1 year	0.9	32	.010
PCS pre op	0.96	61	.070
PCS 6 weeks	0.97	60	.119
PCS 6 months	0.85	48	.000
PCS 1 year	0.92	32	.021
MCS pre op	0.93	61	.001
MCS 6 weeks	0.87	60	.000
MCS 6 months	0.83	48	.000
MCS 1 year	0.80	32	.000
Pain at rest pre op	0.96	59	.041
Pain at rest 6 weeks	0.81	59	.000
Pain walking pre op	0.92	59	.001
Pain walking 6 weeks	0.90	59	.000
Pain stair climb pre op	0.91	59	.000
Pain stair climb 6 weeks	0.87	59	.000
Pain stair descend pre op	0.88	59	.000
Pain stair descend 6 weeks	0.90	59	.000

Table A2: Normality tests for BMI groups

BMI - OKS

		Shapiro-Wilk		
	BMI group	Statistic	Df	Sig.
OKS pre op	non obese = BMI< 30	.970	23	.678
	obese = BMI ≥ 30	.972	38	.452
OKS 6 weeks post op	non obese = BMI< 30	.963	23	.528
	obese = BMI ≥ 30	.968	38	.353
OKS 6 months post op	non obese = BMI<30	.903	17	.075
	obese = BMI ≥ 30	.873	28	.003
OKS 1 year post op	non obese = BMI<30	.884	14	.067
	obese = BMI ≥ 30	.914	18	.102

BMI- SF12

		Shapiro-Wilk		
	BMI group	Statistic	df	Sig.
PCS pre op	non obese = BMI<30	.928	23	.100
	obese = BMI ≥ 30	.970	38	.397
PCS 6 weeks post op	non obese = BMI<30	.943	23	.204
	obese = BMI ≥ 30	.966	37	.305
PCS 6 months post op	non obese = BMI<30	.819	19	.002
	obese = BMI ≥ 30	.862	29	.001
PCS 1 year post op	non obese = BMI<30	.896	14	.098
	obese = BMI ≥ 30	.903	18	.066
MCS pre op	non obese = BMI<30	.929	23	.102
	obese = BMI ≥ 30	.914	38	.006
MCS 6 weeks post op	non obese = BMI<30	.874	23	.008
	obese = BMI ≥ 30	.853	37	.000
MCS 6 months post op	non obese = BMI<30	.790	19	.001
	obese = BMI ≥ 30	.844	29	.001
MCS 1 year post op	non obese = BMI<30	.805	14	.006
	obese = BMI ≥ 30	.796	18	.001

BMI – Pain scores

		Shapiro-Wilk		
	BMI group	Statistic	df	Sig.
pain rest pre op	non obese = BMI<30	.956	23	.382
	obese = BMI ≥ 30	.926	36	.019
pain rest 6 week post op	non obese = BMI<30	.881	22	.013
	obese = BMI ≥ 30	.771	37	.000
pain walking pre op	non obese = BMI<30	.956	23	.393
	obese = BMI ≥ 30	.893	36	.002
pain walking 6 week post op	non obese = BMI<30	.897	22	.026
	obese = BMI ≥ 30	.891	37	.002
pain stair climb pre op	non obese = BMI<30	.923	23	.078
	obese = BMI ≥ 30	.905	36	.005
pain stair climb 6 week post op	non obese = BMI<30	.821	22	.001
	obese = BMI ≥ 30	.889	37	.001
pain stair descend pre op	non obese = BMI<30	.825	22	.001
	obese = BMI ≥ 30	.910	33	.010
pain stair descend 6 week post op	non obese = BMI<30	.891	22	.019
	obese = BMI ≥ 30	.899	36	.003

Table A3: Normality test for WC groups

WC – OKS

		Shapiro-Wilk		
	WC median split groups	Statistic	df	Sig.
OKS pre op	WC ≤ 41.5	.977	31	.731
	WC > 41.5	.968	30	.493
OKS 6 weeks post op	WC ≤ 41.5	.967	31	.446
	WC > 41.5	.961	30	.327
OKS 6 months post op	WC ≤ 41.5	.919	23	.063
	WC > 41.5	.892	22	.021
OKS 1 year post op	WC ≤ 41.5	.876	19	.018
	WC > 41.5	.947	13	.555

WC – SF12

		Shapiro-Wilk		
	WC median split groups	Statistic	df	Sig.
PCS pre op	WC ≤ 41.5	.962	31	.320
	WC > 41.5	.957	30	.253
PCS 6 weeks post op	WC ≤ 41.5	.949	31	.143
	WC > 41.5	.960	29	.329
PCS 6 months post op	WC ≤ 41.5	.785	26	.000
	WC > 41.5	.919	22	.072
PCS 1 year post op	WC ≤ 41.5	.886	19	.028
	WC > 41.5	.925	13	.289
MCS pre op	WC ≤ 41.5	.879	31	.002
	WC > 41.5	.934	30	.064
MCS 6 weeks post op	WC ≤ 41.5	.874	31	.002
	WC > 41.5	.838	29	.000
MCS 6 months post op	WC ≤ 41.5	.786	26	.000
	WC > 41.5	.839	22	.002
MCS 1 year post op	WC ≤ 41.5	.796	19	.001
	WC > 41.5	.888	13	.093

WC- Pain Scores

		Shapiro-Wilk		
	WC median split groups	Statistic	df	Sig.
pain rest pre op	WC ≤ 41.5	.949	31	.149
	WC > 41.5	.895	28	.009
pain rest 6 week post op	WC ≤ 41.5	.873	29	.002
	WC > 41.5	.780	30	.000
pain walking pre op	WC ≤ 41.5	.926	31	.033
	WC > 41.5	.900	28	.011
pain walking 6 week post op	WC ≤ 41.5	.886	29	.005
	WC > 41.5	.902	30	.009
pain stair climb pre op	WC ≤ 41.5	.919	31	.022
	WC > 41.5	.900	28	.011
pain stair climb 6 week post op	WC ≤ 41.5	.793	29	.000
	WC > 41.5	.914	30	.018
pain stair descend pre op	WC ≤ 41.5	.862	30	.001
	WC > 41.5	.902	25	.021
pain stair descend 6 week post op	WC ≤ 41.5	.863	29	.001
	WC > 41.5	.920	29	.030

Table A4: Normality test for WHR groups

WHR – OKS

		Shapiro-Wilk		
	WH median split groups	Statistic	Df	Sig.
OKS pre op	WH ≤ 0.95	.975	32	.647
	WH > 0.95	.976	29	.733
OKS 6 weeks post op	WH ≤ 0.95	.972	32	.554
	WH > 0.95	.965	29	.438
OKS 6 months post op	WH ≤ 0.95	.912	21	.059
	WH > 0.95	.868	24	.005
OKS 1 year post op	WH ≤ 0.95	.912	16	.127
	WH > 0.95	.871	16	.028

WHR – SF12

		Shapiro-Wilk		
	WH median split groups	Statistic	df	Sig.
PCS pre op	WH ≤ 0.95	.972	32	.564
	WH > 0.95	.922	29	.034
PCS 6 weeks post op	WH ≤ 0.95	.933	31	.053
	WH > 0.95	.970	29	.554
PCS 6 months post op	WH ≤ 0.95	.747	24	.000
	WH > 0.95	.882	24	.009
PCS 1 year post op	WH ≤ 0.95	.901	16	.083
	WH > 0.95	.923	16	.189
MCS pre op	WH ≤ 0.95	.907	32	.009
	WH > 0.95	.909	29	.016
MCS 6 weeks post op	WH ≤ 0.95	.854	31	.001
	WH > 0.95	.825	29	.000
MCS 6 months post op	WH ≤ 0.95	.791	24	.000
	WH > 0.95	.821	24	.001
MCS 1 year post op	WH ≤ 0.95	.828	16	.006
	WH > 0.95	.739	16	.000

WHR – Pain Scores

		Shapiro-Wilk		
	WH median split groups	Statistic	df	Sig.
pain rest pre op	WH ≤ 0.95	.965	31	.393
	WH > 0.95	.927	28	.053
pain rest 6 week post op	WH ≤ 0.95	.822	30	.000
	WH > 0.95	.831	29	.000
pain walking pre op	WH ≤ 0.95	.927	31	.036
	WH > 0.95	.894	28	.008
pain walking 6 week post op	WH ≤ 0.95	.824	30	.000
	WH > 0.95	.946	29	.148
pain stair climb pre op	WH ≤ 0.95	.898	31	.006
	WH > 0.95	.913	28	.023
pain stair climb 6 week post op	WH ≤ 0.95	.856	30	.001
	WH > 0.95	.904	29	.012
pain stair descend pre op	WH ≤ 0.95	.884	30	.003
	WH > 0.95	.905	25	.023
pain stair descend 6 week post op	WH ≤ 0.95	.872	30	.002
	WH > 0.95	.885	28	.005

Table A5: Normality test for BF% groups

BF% - OKS

	Body fat median split groups	Shapiro-Wilk		
		Statistic	Df	Sig.
OKS pre op	BF ≤ 39.9	.970	30	.539
	BF > 39.9	.949	30	.164
OKS 6 weeks post op	BF ≤ 39.9	.960	30	.303
	BF > 39.9	.982	30	.885
OKS 6 months post op	BF ≤ 39.9	.863	21	.007
	BF > 39.9	.896	23	.021
OKS 1 year post op	BF ≤ 39.9	.832	13	.017
	BF > 39.9	.930	19	.171

BF% - SF12

	Body fat median split groups	Shapiro-Wilk		
		Statistic	df	Sig.
PCS pre op	BF ≤ 39.9	.938	30	.078
	BF > 39.9	.955	30	.227
PCS 6 weeks post op	BF ≤ 39.9	.953	30	.199
	BF > 39.9	.968	29	.499
PCS 6 months post op	BF ≤ 39.9	.886	22	.015
	BF > 39.9	.819	25	.000
PCS 1 year post op	BF ≤ 39.9	.855	13	.033
	BF > 39.9	.938	19	.246
MCS pre op	BF ≤ 39.9	.909	30	.014
	BF > 39.9	.922	30	.030
MCS 6 weeks post op	BF ≤ 39.9	.929	30	.045
	BF > 39.9	.820	29	.000
MCS 6 months post op	BF ≤ 39.9	.828	22	.001
	BF > 39.9	.796	25	.000
MCS 1 year post op	BF ≤ 39.9	.743	13	.002
	BF > 39.9	.809	19	.002

BF% - Pain Scores

	Body fat median split groups	Shapiro-Wilk		
		Statistic	df	Sig.
pain rest pre op	BF ≤ 39.9	.939	29	.093
	BF > 39.9	.944	29	.124
pain rest 6 week post op	BF ≤ 39.9	.855	29	.001
	BF > 39.9	.730	29	.000
pain walking pre op	BF ≤ 39.9	.900	29	.010
	BF > 39.9	.938	29	.091
pain walking 6 week post op	BF ≤ 39.9	.897	29	.008
	BF > 39.9	.860	29	.001
pain stair climb pre op	BF ≤ 39.9	.925	29	.040
	BF > 39.9	.893	29	.007
pain stair climb 6 week post op	BF ≤ 39.9	.880	29	.003
	BF > 39.9	.867	29	.002
pain stair descend pre op	BF ≤ 39.9	.817	27	.000
	BF > 39.9	.912	27	.025
pain stair descend 6 week post op	BF ≤ 39.9	.898	28	.011
	BF > 39.9	.889	29	.005

Table A6: Normality test for US groups

US - OKS

		Shapiro-Wilk		
	US1mediansplit	Statistic	Df	Sig.
OKS pre op	1.00	.968	30	.483
	2.00	.974	31	.640
OKS 6 weeks post op	1.00	.963	30	.360
	2.00	.973	31	.619
OKS 6 months post op	1.00	.819	21	.001
	2.00	.911	24	.037
OKS 1 year post op	1.00	.802	15	.004
	2.00	.934	17	.250

US - SF12

		Shapiro-Wilk		
	US1mediansplit	Statistic	df	Sig.
PCS pre op	1.00	.957	30	.254
	2.00	.957	31	.248
PCS 6 weeks post op	1.00	.951	30	.185
	2.00	.950	30	.171
PCS 6 months post op	1.00	.866	23	.005
	2.00	.750	25	.000
PCS 1 year post op	1.00	.838	15	.012
	2.00	.956	17	.559
MCS pre op	1.00	.890	30	.005
	2.00	.934	31	.057
MCS 6 weeks post op	1.00	.883	30	.003
	2.00	.864	30	.001
MCS 6 months post op	1.00	.815	23	.001
	2.00	.825	25	.001
MCS 1 year post op	1.00	.695	15	.000
	2.00	.845	17	.009

US – Pain scores

		Shapiro-Wilk		
	US1mediansplit	Statistic	df	Sig.
pain rest pre op	1.00	.928	29	.050
	2.00	.959	30	.297
pain rest 6 week post op	1.00	.825	29	.000
	2.00	.786	30	.000
pain walking pre op	1.00	.927	29	.047
	2.00	.907	30	.013
pain walking 6 week post op	1.00	.910	29	.017
	2.00	.852	30	.001
pain stair climb pre op	1.00	.932	29	.060
	2.00	.886	30	.004
pain stair climb 6 week post op	1.00	.867	29	.002
	2.00	.862	30	.001
pain stair descend pre op	1.00	.836	26	.001
	2.00	.915	29	.023
pain stair descend 6 week post op	1.00	.874	28	.003
	2.00	.903	30	.010

Appendix C: Participant Information Sheets and Consent Form

Appendix D: Copy of Questionnaires Used

Appendix E: Copy of Retrospective review paper accepted for publication